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# EVALUATION AND REMEDIATION OF SOCIAL ATTENTION PROCESSES IN PRESCHOOLERS WITH AUTISM SPECTRUM DISORDER

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par

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de Roncq (FRANCE)

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# DOCTORAT EN NEUROSCIENCES

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Thèse de

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Intitulée

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# Résumé

Les troubles du spectre autistique (TSA) sont une famille de troubles neurodéveloppementaux incluant des difficultés de communication, des interactions sociales ainsi que la présence de comportements répétitifs et intérêts restreints. Ils touchent actuellement environ 1 enfant sur 36 et ce nombre croît depuis des années. Cette importante prévalence a notamment encouragé de nombreuses recherches concernant l'étiologie mais également la pathogenèse des TSA.

Parmi les courants de pensée tentant d'expliquer les TSA et leurs origines, la théorie de la motivation sociale s'est fait une place au fil du temps et constitue un courant de pensée majeur dans le domaine. Cette dernière stipule que les enfants avec TSA auraient une appétence moins importante à s'orienter vers les stimuli sociaux. Cette moindre orientation vers le social, en lien avec un récompense perçue moins grande, entraînerait une diminution des compétences sociales, de l'apprentissage par les pairs dans les plus jeunes années, et engendrerait des connexions cérébrales atypiques. En effet, l'enfance est une période où le cerveau est très adaptable (dit plastique), car il forme, renforce et élimine des connexions entre les neurones en fonction de la fréquence de stimulation. Ainsi, il est suggéré que par la sous-stimulation des connexions synaptiques importantes dans le développement des compétences psycho-sociales, celles si soient éliminées alors que d'autres connexions, comme celles en lien avec les routines sensorielles soient renforcées par une stimulation plus fréquente. En résumé, le manque d'intérêt pour leur environnement social dans l'enfance aurait un effet boule de neige sur le développement et serait la cause du développement des TSA. Corroborant cette théorie, de nombreuses études ont utilisées la technologie de l' « eye-tracking », ou oculométrie, outil permettant d'enregistrer où une personne regarde grâce à des capteurs infrarouges. Via de nombreuses études, la recherche a pu prouver qu'il existait bel et bien un biais pour le social dans l'exploration visuelle des enfants avec un développement typiques, que l'on ne retrouve pas chez les enfants ayant développés, voire qui développeront, des symptômes autistiques.

L'objectif de mon projet de thèse était de mieux comprendre cette orientation sociale atypique chez les enfants TSA mais également de mieux comprendre les implications de cette dernière dans le développement précoce, notamment chez les enfants recevant une intervention précoce. Enfin, une dernière partie de mon projet de thèse a été dédié à la création d'un essai clinique visant à remédier l'orientation sociale des enfants via l'utilisation de l'eye-tracking de manière active.

Ma première étude a cherché à identifier les prédicteurs d'évolution chez des enfants TSA recevant une intervention précoce intensive spécifique aux TSA ou une intervention communautaire (par exemple, orthophonie, psychomotricité). L'âge s'est révélé être le facteur le plus important, car un plus jeune âge au début de l'intervention était associé à une réduction plus importante des symptômes et une augmentation des compétences cognitives plus significative après un an d'intervention. L'orientation sociale a été identifiée comme un modérateur majeur de la réponse à l'intervention, les enfants les plus attentifs à leur environnement social au début de l'intervention progressant le plus rapidement.

La deuxième étude a examiné les trajectoires de développement, notamment cognitives, des enfants après deux ans d'intervention précoce intensive. Trois profils de développement ont été identifiés, approfondissant ainsi notre compréhension de l'hétérogénéité de la réponse à l'intervention chez les enfants TSA. Malgré des difficultés à pouvoir efficacement prédire quels enfants progresseraient ou non, cette étude a montré que les enfants qui faisaient des progrès précoces continuent de progresser. Les implications cliniques sont importantes, notamment en ce qui concerne l'adaptation des interventions pour les enfants ayant un profil de compétences plus bas et ne montrant que peu de changements en début d'intervention.

Mes études suivantes se sont concentrées sur l'eye-tracking pour mieux comprendre l'orientation sociale. La première étude a comparé l'exploration visuelle des enfants TSA à celle des enfants neurotypiques avec des scènes sociales de complexité variable. Les résultats ont montré des différences dans l'exploration des zones sociales importantes et une modification de la dynamique d'exploration en fonction de la complexité sociale. De plus les résultats ont indiqué une relation entre l'exploration visuelle et le profil développemental.

Ma deuxième étude en eye-tracking a évalué l'orientation sociale à l'aide de stimuli sous forme de "cartoons". L'idée était de réinterpréter les tâches d'orientation sociale actuelles en minimisant les biais. Les résultats ont montré que les enfants préféraient tous les stimuli sociaux dans cette tâche, mais avec des différences dans la manière de regarder liées au profil développemental des enfants. Des résultats préliminaires chez des enfants à risque ont également montré une certaine sensibilité à ces stimuli sociaux cartoonesques, avec notamment les enfants à risque montrant une orientation sociale plus limitée.

Dans ma dernière étude en eye-tracking j'ai voulu comparer l'exploration visuelle de visages en fonction de leur degré de réalisme (cartoons, avatars, réalistes) chez des enfants TSA et neurotypiques. Les résultats montraient que les enfants des deux groupes modifiaient leur exploration de manière similaire en fonction du degré de réalisme. Les stimuli de type dessin animé semblaient être les plus intéressants pour les enfants, tandis que les avatars semblaient induire une exploration atypique chez tous nos enfants. Les résultats supportent l'utilisation de stimuli de cartoonesques lors de protocoles de remédiation en réalité virtuelle par exemple, puisque les enfants TD et TSA les explorent de manière similaire.

Pour finir, toutes ces études m'ont permis d'imaginer un moyen d'augmenter l'orientation sociale chez les enfants avec TSA. En effet, si cette dernière est la cause et module grandement la réponse à l'intervention, alors il m'apparaissait primordial d'essayer d'augmenter cette orientation sociale. J'ai pour cela utilisé l'eye-tracking, mais cette fois de manière active via des paradigmes dits « gaze-contingent ». Ces derniers permettent à la personne qui regarde l'écran d'activer les stimuli via le regard. Les résultats préliminaires de cette étude clinique, toujours en cours, semblent aller dans le sens de nos hypothèses.

# Abstract

Autism Spectrum Disorders (ASD) are a group of neurodevelopmental disorders that encompass communication difficulties, social interaction challenges, and the presence of repetitive behaviors and restricted interests. Currently, about 1 in 36 children are affected by ASD, and this number has been increasing for the past decade. This high prevalence has spurred extensive research into the etiology and pathogenesis of ASD.

Among the theories attempting to explain ASD and their origins, the “Social motivation theory” (Chevallier et al., 2012) has gained prominence over time. This theory posits that children with ASD have less motivation to engage in social stimuli. This reduced social engagement, related to lower perceived rewards, leads to diminished social skills, decreased peer learning in early years, and atypical brain connections. Indeed, childhood is a period of significant brain plasticity, with synaptic connections forming, strengthening, and being eliminated based on the frequency of stimulation. It is suggested that the under-stimulation of networks crucially involved in psychosocial development leads to their elimination, while other connections, such as those related to sensory routines, are strengthened by increased stimulation. In summary, a lack of interest in the social environment during childhood has a snowball effect on development, resulting in the emergence of ASD symptoms. Supporting this theory, numerous studies using eye-tracking technology have shown bias for social stimuli within the visual exploration of typically developing children, which is not always observed in children with, or at risk for, ASD.

The aim of my project was to better understand atypical social orientation in children with ASD and its implications in early development, especially in children receiving early intensive interventions. Additionally, part of my thesis project was dedicated to designing a clinical trial to remediate social orientation in children using eye-tracking actively.

My first study sought to identify predictors of progress in children with ASD receiving either intensive early intervention specifically designed for ASD or community-based intervention. Age proved to be the most crucial factor, as a younger age at the start of intervention was associated with a greater reduction in symptoms and a more significant increase in cognitive skills after one year of intervention. Social orientation was identified as a major moderator of intervention response, with children more attentive to their social environment at baseline progressing more quickly.

The second study examined the developmental trajectories, particularly cognitive, of children after two years of early intensive intervention. Three developmental profiles were identified, further deepening our understanding of heterogeneity in response to intervention among children with ASD. Despite challenges in effectively predicting which children would exhibit cognitive gains or not, this study showed that children who made early progress continued to. The clinical implications are significant, especially in terms of adapting interventions for children with a lower skill profile and showing only minor changes at the

beginning of the intervention.

My subsequent studies focused on eye-tracking to better understand social orientation mechanisms. The first study compared the visual exploration of children with ASD to that of neurotypical children using social scenes of varying complexity. The results revealed differences in the exploration of important social areas and a change in exploration dynamics depending on social complexity. Additionally, the findings indicated a relationship between visual exploration and the developmental profile of the children.

In my second eye-tracking study, social orientation was assessed using stimuli in the form of "cartoons". The idea was to reinterpret current social orientation tasks while minimizing biases. The results showed that all children preferred social stimuli in this task, but with differences in viewing patterns related to the children's developmental profiles. Preliminary findings in at-risk children also demonstrated some sensitivity to these cartoon-like social stimuli, with at-risk children exhibiting more limited social orientation.

In my final eye-tracking study, I compared the visual exploration patterns of faces based on their degree of realism (cartoons, avatars, realistic) from children with ASD and neurotypical children. Results showed that children in both groups adjusted their exploration similarly based on the degree of realism. Cartoon-like stimuli appear to be the most interesting for children, while the avatar condition seemed to induce atypical exploration in all our children. Results support the use of cartoonish stimuli in virtual reality remediation protocols, as both typically developing, and children with ASD explore them similarly.

Finally, these studies have allowed me to think about ways to increase social orientation in children with ASD. Indeed, if social orientation is a cause and greatly modulates the response to intervention, then it seemed essential to me to try to increase it somehow. To do this, I used eye-tracking again, but this time actively through "gaze-contingent" paradigms, which allow the person watching the screen to control what happens using their gaze. I present here the extremely preliminary results of this clinical trial. As of now, these results appear in line with our hypothesis, but more participants are needed.

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# 1 – Introduction

## 1.1 Autism Spectrum Disorders

In this opening section, we will delve into the disorders that form the core focus of this work. We will provide an overview of their etiology, explore the primary theories attempting to unravel symptomatology, and discuss the various interventions that have been developed in response. All these topics will be examined in the context of their historical development and from the perspective of their evolution over time.

### *1.1.1 History and definition*


**Figure 1** – Photographs of Hans Asperger on the left side and Leo Kanner on the right side.

Just like everything else, Autism Spectrum Disorders (ASD) have a story. This one begins in the 1940s when two psychiatrists described, at about the same time, individuals with peculiar clinical manifestations, that will later be considered to be the diagnostic symptoms of ASD. In his seminal paper , Léo Kanner (see Fig.1; 1943) described 11 children under 11 years of age, all sharing the same symptomatology. In particular, he reported on the father's portrayal of little Donald, a 5-year-old child whose behavior was questioning his family. The little boy was described as follows: "*He seems to be self-satisfied. He has no apparent affection when petted. He does not observe the fact that anyone comes or goes, and never seems glad to see father of mother or any playmate. He seems almost to draw into his shell and live within himself. [...] He seldom comes to anyone when called but has to be picked up and carried or led wherever he ought to go. [...] developed a mania for spinning blocks and pans and other round objects."*. Years before but only published in 1944, Hans Asperger (see Fig.1) described 4 children that are "*particularly interesting and highly recognizable*". The first boy, a little Fritz, was described in the following terms "*From the earliest age Fritz never did what he was told. [...] He was restless and fidgety. [...] He was never able to become integrated into a group of playing children. He never got on with other children and, in fact, was not interested in them. [...] Although he acquired language very early, it was impossible to teach him the polite form of address. [...] Another strange phenomenon in this boy was the occurrence of certain stereotypic movements and habits."*. Of course, the children described in these seminal reports were not the first to exhibit these symptoms, but it was the first time that someone merged these symptoms into a distinct and unique diagnostic entity. At the time, these symptoms were typically regarded as mental retardation, psychotic behaviors, or included in any other diagnosis that could account for a portion of these atypical behaviors. Consequently, the early descriptions by Kanner and Asperger significantly impacted the history of ASD, notably by using the term "Autism" for the first time and by accurately describing the social difficulties shared among children. However, despite the social challenges faced by all the children described, the vast diversity of profiles within their small samples led to the classification of autism as described by Kanner and Asperger into two distinct entities for many years. Indeed, the children described by Kanner all seemed to have considerable difficulties with language, struggling to understand its meaning or using it in an unconventional manner. In contrast, children described by Asperger appeared to speak in a sophisticated manner, employing language to discuss topics in which they had become experts. It was not until 2013, 70 years after these initial descriptions of autistic symptoms, that Kanner's and Asperger's autism were combined under the umbrella term "Autism Spectrum Disorders" with the revision of diagnostic criteria and the concept's review in the DSM-5 (American Psychiatric Association, 2013). This new classification resulted from years of research that gradually highlighted the existence of a spectrum in autism, with individuals sharing common core symptoms but exhibiting extremely diverse clinical manifestations.

Today, according to the updated classification in the DSM-5, ASD are defined as a group of neurodevelopmental disorders characterized by persistent difficulties in communication and social interaction, as well as restricted and repetitive patterns of behavior, interests, or activities (American Psychiatric Association, 2013; see subsection 1.1.3 for detailed diagnostic criteria). The prevalence of ASD in the global population reached 1 in 54 in 2020 (see Fig.2; Maenner et al., 2020), representing a 787% incidence increase from 1998 to 2018 (Russell et al., 2022). While one might hope for a slowdown in this rapid growth in the coming years, recent data has revealed an even higher prevalence of 1 in 36 in 2023. This latest information also provides new evidence for a higher prevalence of ASD diagnoses in young white children compared to black children, which is unprecedented. The sex ratio has always been and continues to be higher for males, as they are 3.8 times more likely to be

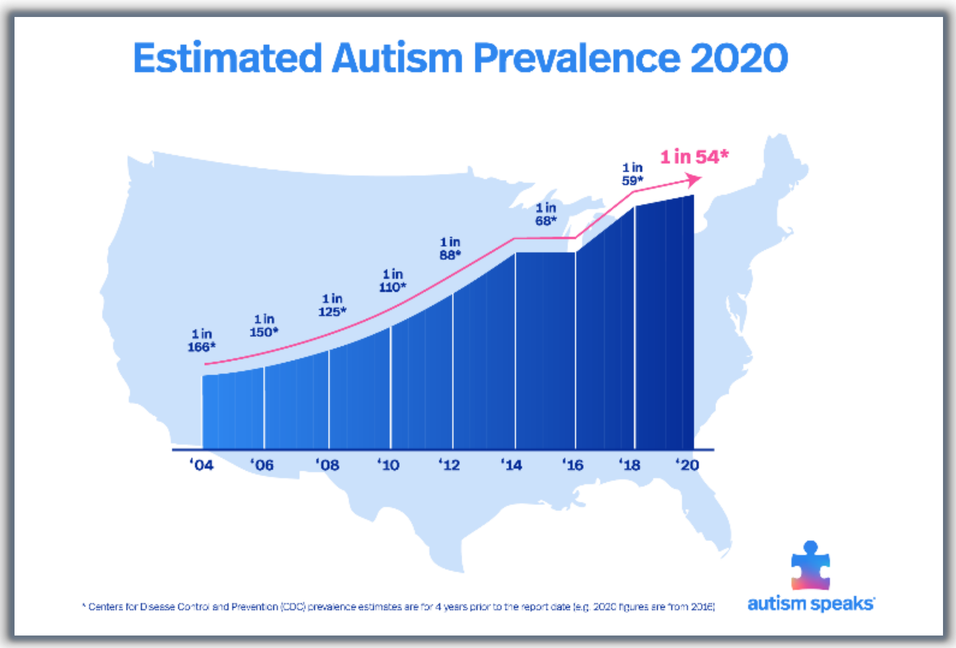


**Figure 2** - Estimated ASD prevalence in 2020 (Maenner et al.2020)

diagnosed with ASD than females. This imbalance is the subject of extensive research and is partially explained by what is called the "female phenotype" (Dean et al., 2017; Lai et al., 2015), which includes less obvious and more socially oriented symptoms compared to those typically exhibited by males, making it hard to diagnose and easier to miss for clinicians.

We previously mentioned that ASD were once commonly diagnosed as intellectual retardation. This is due to the high prevalence of intellectual disabilities as a comorbidity. Recent data reports that approximately 37.9% of individuals with ASD have an IQ below 70 (Maenner, 2023), which is generally considered the threshold for intellectual disability, with a higher prevalence observed in black children. The rapid increase in the incidence of autism over the years has been widely discussed and is often thought to reflect the result of numerous societal changes and factors, rather than an actual increase in ASD cases. Indeed, this growth is mostly attributed to increased communication about the diagnosis, broader application of diagnostic criteria across populations over time, improved knowledge leading to heightened awareness, enhanced diagnostic tools, previously missed diagnoses being identified, and greater societal acceptance of what was once a daunting diagnosis. Collectively, these factors might explain the rising prevalence of ASD worldwide over the past decades.

### 1.1.2 Etiology

"*But what causes ASD?*" This is by far the most common question I've encountered over the past few years when discussing my work with others. Regrettably, reading this work won't provide a definitive answer, as repeating "*We still don't know exactly*" didn't yield any new insights. Indeed, despite extensive research on the subject, the etiology of ASD remains unknown. Of course, we have gathered clues and evidence for various interacting factors contributing to ASD, but not enough to offer a single, solid explanation.

Parental age is one of the most frequently reported risk factors for autism (Brandt et al., 2019; Kavanaugh et al., 2022; Wu et al., 2017). Over the years, evidence has shown that increased maternal age at birth is associated with prolonged exposure to toxins (Maramara et al., 2014), which might affect the child's future development, or even a greater risk of chromosomal anomalies in the child, compromising typical development (Salem Yaniv et al., 2011). However, even greater risks are generally associated with advanced paternal age. Older paternal age is linked to increased risks of miscarriage, pathogenic genetic mutations, childhood cancers, congenital anomalies, psychiatric diseases, or complications such as fetal deaths (for a review see Brandt et al., 2019). A review and meta-analysis by Wu et al., (2017) comprising 27 studies with a total of 17,658,960 participants, highlighted that the risks of ASD increased by 41% with higher maternal age and by 51% with higher paternal age. Today, the mechanism underlying the link between increased risk for developing neurodevelopmental disorders and higher parental age remains poorly understood. However, this topic is currently crucial in light of the increase in life expectancy (see Fig.3) and the global trend towards childbearing at a later age (Brandt et al., 2019; Bray et al., 2006; WHO, 2022).

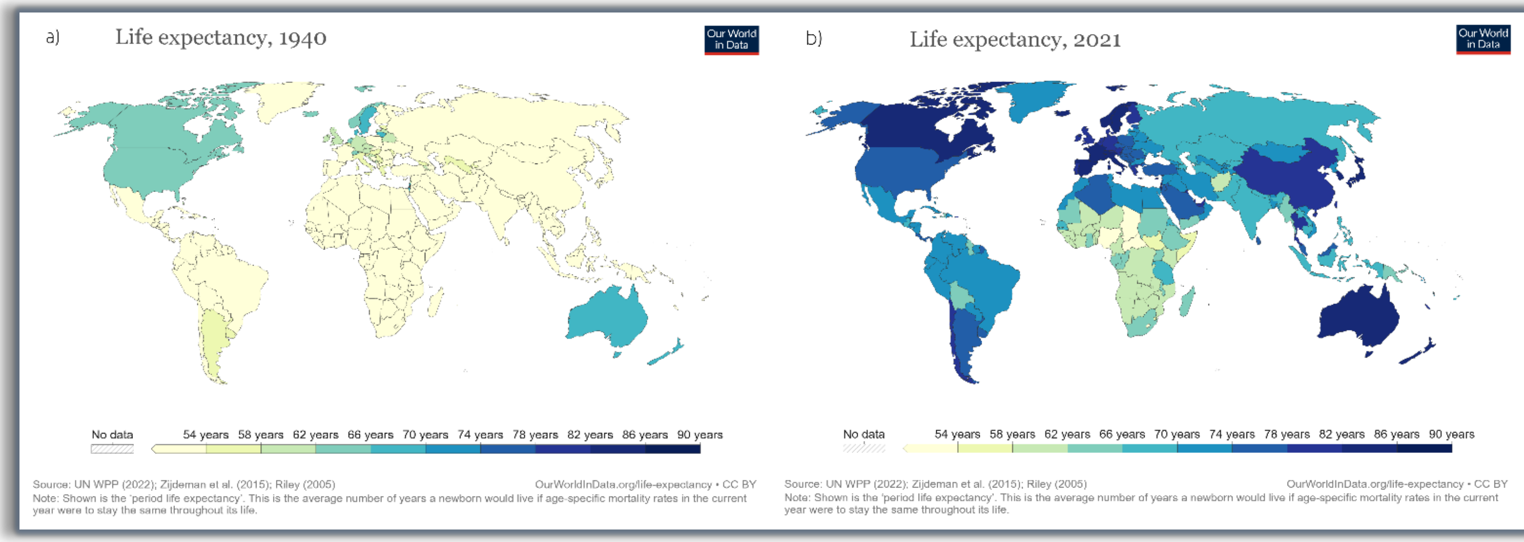


**Figure 3** - Maps of the life expectancy by country **a)** Worldwide life expectancy in 1940 **b)** Worldwide life expectancy in 2021. **More contrasted colors represent higher life expentancy*

Many environmental factors have been implicated in the pathogenesis of ASD. For instance, exposure to air pollutants during childhood, such as polycyclic aromatic hydrocarbons (PAHs), traffic-related air pollution, and metals such as mercury and arsenic, has all been linked as potential risk factors of ASD (Woodward et al., 2015). Additionally, as mentioned earlier, exposure to chemicals during the gestational period might also lead to increased risks of ASD. For example, exposure to chlorpyrifos, commonly found in insecticide products, during pregnancy induced autism-like deficits in mouse model studies (Lan et al., 2017). Other studies showed that children living in homes with polyvinyl chloride flooring, a significant source of phthalates, exhibited increased risks for ASD diagnoses (Larsson et al., 2009) or reported higher scores on the Social-Responsiveness Scale-II (SRS-II), a tool frequently used in autism research to measure social impairment (Miodovnik et al., 2011; Oulhote et al., 2020). Conversely, it is worth noting that some chemicals, particularly folic acid, seem to have a protective effect on the development of ASD. Studies have shown a negative relationship between the amount of folic acid supplementation taken by mothers during pregnancy and the risks of developing autism in their offspring (Goodrich et al., 2018; Oulhote et al., 2020).

Genetics is another well-established risk factor for autism. In 1977, the first twin study of autism conducted by Folstein & Rutter showed a predominantly genetic contribution to autism as they evidenced a 36% concordance rate for autism in monozygotic twins compared to a 0% concordance for dizygotic twins. This groundbreaking study set the stage for numerous family and twin studies to investigate the genetic component of autism. The most recent meta-analysis of all published twin studies of autism spectrum disorder conducted by Tick et al., (2016) yielded a heritability estimate of 64-91% with minimal to no significant shared environmental effect. These twin studies provide strong evidence of a mainly genetic contribution to ASD and more negligible shared environmental effects. To date, more than 300 genes have been indexed as syndromic and an even higher number of 1300 genes have been indexed as potentially implicated in the development of ASD in the SFARI Gene database (SFARI, 2023). Despite the now indisputable link between genetics and ASD, more research is still needed to understand the underlying mechanisms and especially its interaction with environmental factors, remaining at the very heart of many research and debates.

Indeed, it is likely that it is an interplay of genetic and environmental factors that causes ASD and not just one or the other (Carter & Blizard, 2016; Cheroni et al., 2020; Dunaway et al., 2016; Modafferi et al., 2021). This idea is especially supported by studies such as the one by Mazina et al., (2015), pointing to interaction effects between the presence of ASD-associated copy number variations (CNV) and prenatal maternal infection, or by Kim et al., (2017) showing an interaction between the number of CNV and air pollution, leading to an increased risk for autism. Other studies evidenced that more than 4000 chemicals interact with one or more genes associated with autism when investigating more than 200 genes and 10.000 chemicals (Carter & Blizard, 2016), making these interaction very likely to occur during development. Finally, even twin studies brought their part of support as monozygotic twins do not necessarily both develop ASD symptoms over time, hinting once again at a potential interaction between genes and environmental factors.

Finally, I would like to end this paragraph on risk factors by discussing vaccines, which is another frequently investigated potential environmental factor. Addressing this subject appears crucial to me in the context of the recent COVID-19 pandemic, but more generally to participate in the spreading of scientific fact-based knowledge. Indeed, vaccines are frequently considered by many as the primary cause of autism, most of the time based on rumors and theories in the absence of any scientific background. I have myself often been asked during my years of practice if vaccines cause autism. I have met many families refusing to immunize their child because of the diagnosis of the older brother and the association made between this diagnosis and the vaccines preceding it. So, what about this myth? The latter originates from a publication dating from 1998 and pointing out a relationship between the measles, mumps, and rubella vaccine (MMR) and ASD. However, the study had a small sample size, and the findings were later discredited due to methodological flaws, undisclosed conflicts of interest, and ethical violations. Many studies have since documented numerous findings that refute this association. One of the first studies in response to the original publication was the one by Taylor et al., (1999). In this study, the authors collected data from almost 500 children with autism in the UK to retrospectively investigate the causal association with MMR vaccines and the development of ASD. They found no temporal association between the MMR vaccination and the onset of autism within 1 to 2 years after the vaccination. There was also no significant clustering of developmental regression in the months following the vaccines. More recently, a meta-analysis including five cohort studies and five case-control studies gathered data from respectively 1,256,407 and 9,920 children. The cohort data showed that there was no relationship between autism and MMR vaccine, thimerosal, or mercury exposure. The case-control data also did not find any evidence for an increased risk of developing autism following MMR, thimerosal, or mercury exposure when grouped by condition or exposure type (L. E. Taylor et al., 2014). Overall, in view of the numerous scientific data

(Gabis et al., 2022; Hviid et al., 2019; Madsen et al., 2002; B. Taylor et al., 1999; L. E. Taylor et al., 2014; Uno et al., 2012), vaccines are currently not considered as a risk factor for autism. Nowadays, vaccines prevent around 2 to 3 million children deaths every year (Muhoza et al., 2021) whereas non-vaccination sometimes leads to dramatic consequences on young children (Zucker et al., 2020).

### *1.1.3 ASD diagnosis*

Now that we have briefly addressed the symptomatology, history, and etiology of ASD, we will turn our attention to the process of diagnosing autism in a clinical setting. As mentioned earlier, the absence of a definitive genetic cause renders genetic testing an unsuitable method for diagnosis. Indeed, ASD cannot be diagnosed using genetic testing or any other test that would yield an unambiguous result. Primarily, the diagnosis of ASD depends on careful observation and clinical judgment, which is why it can be quite challenging in practice. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5), symptoms must include persistent deficits in social communication and social interaction, as well as restricted and repetitive behaviors. These symptoms must have been present during the early developmental period and cause significant impairment in social, occupational, or other areas of functioning. Moreover, they should not be better explained by intellectual disability or global developmental delay.

## DSM-5 diagnostic criteria for Autism Spectrum Disorders

A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by all the following, currently or by history*

1. Deficits in social-emotional reciprocity (abnormal social approach, failure of back-and-forth conversation; reduced sharing of interests/emotions/affect; failure to initiate/respond to social interactions)
2. Deficits in nonverbal communicative behaviors used for social interaction (poorly integrated verbal and nonverbal communication; abnormalities in eye contact and body language/deficits in understanding and use of gestures; total lack of facial expressions and nonverbal communication)
3. Deficits in developing, maintaining, and understanding relationships (difficulties adjusting behavior to suit various social contexts; difficulties in sharing imaginative playmaking friends; absence of interest in peers)

B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history*

1. Stereotyped or repetitive motor movements, use of objects, or speech (motor stereotypes, lining up toys or flipping objects, echolalia, idiosyncratic phrases)
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day)
3. Highly restricted, fixated interests that are abnormal in intensity or focus (strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests)
4. Hyper-/hypo-reactivity to sensory input or unusual interest in sensory aspects of the environment (apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement)

*Specify current severity

C. Symptoms must be present in the early developmental period.

D. Symptoms cause clinically significant impairment in social, occupational, or other areas of current functioning.

E. Impairments are not better explained by intellectual disability or global developmental delay.

Specify if:

1. With/without intellectual and/or language impairment
2. Associated with a known medical/genetic condition/environmental factor
3. Associated with another neurodevelopmental/mental/behavioral disorder
4. With/without catatonia

Over time, various diagnostic assessment tools have been introduced to provide a better sense of the threshold for diagnosis and, to some extent, a way to quantify the "severity" of symptoms. However, even these diagnostic aids do not offer an infallible answer, particularly because they lack specificity (e.g., sensitivity to other developmental disorders). In the end, clinical judgment and knowledge always prevail when diagnosing autism.

**Figure 4** - Autism Diagnostic Observation Schedule – 2nd Edition material (Lord et al. 2012)

The Autism Diagnostic Observation Schedule, 2nd Edition (ADOS-2; Lord et al., 2012; see Fig.4) is one of the two most widely recognized assessments for ASD diagnosis. This gold standard tool comprises a semi-structured, standardized assessment that includes several play-based activities designed to gather information in the areas of communication, reciprocal social interactions, and restricted and repetitive behaviors. During the assessment, the clinician proposes a series of activities to obtain language samples, elicit social interaction, or offer play with toys that may provoke sensory behaviors. This assessment consists of different versions, referred to as "modules" each addressing different ages and developmental levels. It can be used to assess children from 12 months of age (using the Toddler module) up to adults (using the 4th module). Each module is designed to challenge the participant according to their developmental level. The lower modules focus on non-verbal communication, such as pointing, while higher modules assess the participant's understanding of abstract concepts like emotions or social relationships. Ultimately, the ADOS-2 includes a diagnostic algorithm that summarizes the most relevant items of the evaluation in the Social Affect scale (SA, encompassing communication and social interaction) and the Restricted and Repetitive Behavior scale (RRB). By adding these two domains, we obtain a total score reflecting the level of observed symptoms and compare it to the appropriate threshold, depending on the module and language level. A participant with a total score at or above the threshold is highly likely to be diagnosed with ASD, in the absence of any other diagnosis that would better explain the symptoms. The ADOS-2 is the most widely used tool in both clinical practice and research. Its use in research is primarily due to the development of the ADOS calibrated severity score algorithms (Gotham et al., 2009; Hus et al., 2014), which allow for the assessment of RRB, SA, and total symptom severity. These calibrated scores differ from the ADOS-2 algorithm total, as they enable comparisons of children with various developmental and language levels (across modules and editions of the ADOS). They are the most frequently used indicator of progress regarding ASD symptomatology within the literature. This usage, however, is debated and even discouraged by the AADOS creators as the test was not designed with this purpose in mind.

The second gold standard assessment is the Autism Diagnostic Interview – Revised (ADI-R, Lord et al., 1994). This semi-structured interview is typically administered to parents or caregivers and consists of a series of questions about the individual's development, behavior, and social communication skills, both currently and during infancy (when applicable). The questions are organized into several domains, including social interaction, communication, repetitive behaviors, and the onset of symptoms during development. The ADI-R is often used in conjunction with the ADOS-2 to provide a comprehensive evaluation of an individual's symptoms and behaviors.

A recent meta-analysis including around 30 studies and more than 66.000 individuals with ASD from 35 countries in the world reported a mean age at diagnosis of around 60 months of age (van 't Hof et al., 2021). While this age at diagnosis has decreased significantly over the past decades due to increased awareness and knowledge in the field of ASD, it remains alarmingly high at the same time considering current guidelines advocate for early intervention, ideally before 3-years-of-age (Bejarano-Martín et al., 2020; Fuentes et al., 2021; Landa, 2018; National Research Council, 2001; Zwaigenbaum et al., 2015) to benefit from early cerebral plasticity (Dawson, 2008; Ismail et al., 2017). Improving early diagnosis remains a major challenge requiring the development of better diagnostic tools or more research in the identification of predictive biomarkers during pre-symptomatic stages for example.

### *1.1.4 Theorical frameworks*

Similar to the etiology of ASD, pathogenesis is extensively documented but not yet fully understood. The development of symptomatology has been the subject of numerous theories. In this section, we will briefly introduce some of these theories, particularly those with significant influence on the present work or supported by the results of my studies. It should be noted, however, that other theories exist, such as the "broken mirrors theory" (Ramachandran & Oberman, 2006) or the "extreme male brain theory" (Baron-Cohen, 2002), which will not be discussed here.

During the 1980s, the golden age of cognitivism, numerous theories attempted to explain ASD by a cognitive deficit focused on one specific domain. One particularly intriguing theory proposes an underlying executive/attentional dysfunction as the primary mechanism behind ASD symptoms (Ozonoff et al., 1991). This theory has been supported by many studies in the literature that link ASD and Attention Deficit Hyperactivity Disorder (ADHD), as they share common underlying mechanisms in terms of attentional/executive dysfunctions (Allen & Courchesne, 2001; Antshel & Russo, 2019; Berenguer et al., 2018; Brieber et al., 2007), even at early developmental stages (Zwaigenbaum et al., 2005). The high proportion of ADHD diagnosis within the ASD population (more than 20%, Lai et al., 2019) further supports this view. I find this theory interesting because it can be relatively easily studied through eye-tracking research, as eye movements accurately reflect attentional processes. For example, visual disengagement, a basic attentional skill that is dysfunctional in ASD, can be readily studied using eye-tracking (Frick et al., 1999; Goold et al., 2022; Kikuchi et al., 2011; Landry & Bryson, 2004; Sacrey et al., 2014). However, this theory of executive dysfunction as the source of autism symptomatology does not account for the heterogeneity of autism (Farhat et al., 2022), particularly considering the large number of individuals who do not exhibit attentional difficulties at all, even at very basic levels. As a result, these theories were eventually discarded in favor of less domain-specific theories.

One of these theories is the "Social Motivation theory" (Chevallier et al., 2012; see Fig.5). This theory emerged from the evolving understanding of autism over the years. ASD were initially perceived as a single entity with a unique symptomatology but later perceived as a continuum with diverse presentations. This change in perception, notably illustrated by the significant differences in diagnostic criteria during the transition from DSM-IV to DSM-5, has influenced theories that now aim to provide a general explanation of symptoms rather than individual characteristics. The "Social Motivation theory", proposed by Chevallier et al. (2012), posits that the core underlying factor of ASD is a diminished social motivation. The theory elaborates social motivation as an interplay of psychological dispositions and biological mechanisms that collectively predispose an individual to favor the social world over non-social environments. This predisposition can be further divided into three components: Social orienting: the innate inclination to attend to and engage with social stimuli, such as faces, voices, and gestures; Social reward: the inherent drive to seek out and derive pleasure from social interactions, which facilitates the formation and reinforcement of social bonds; Social maintaining: the ongoing effort to nurture and preserve social relationships, demonstrating a commitment to social

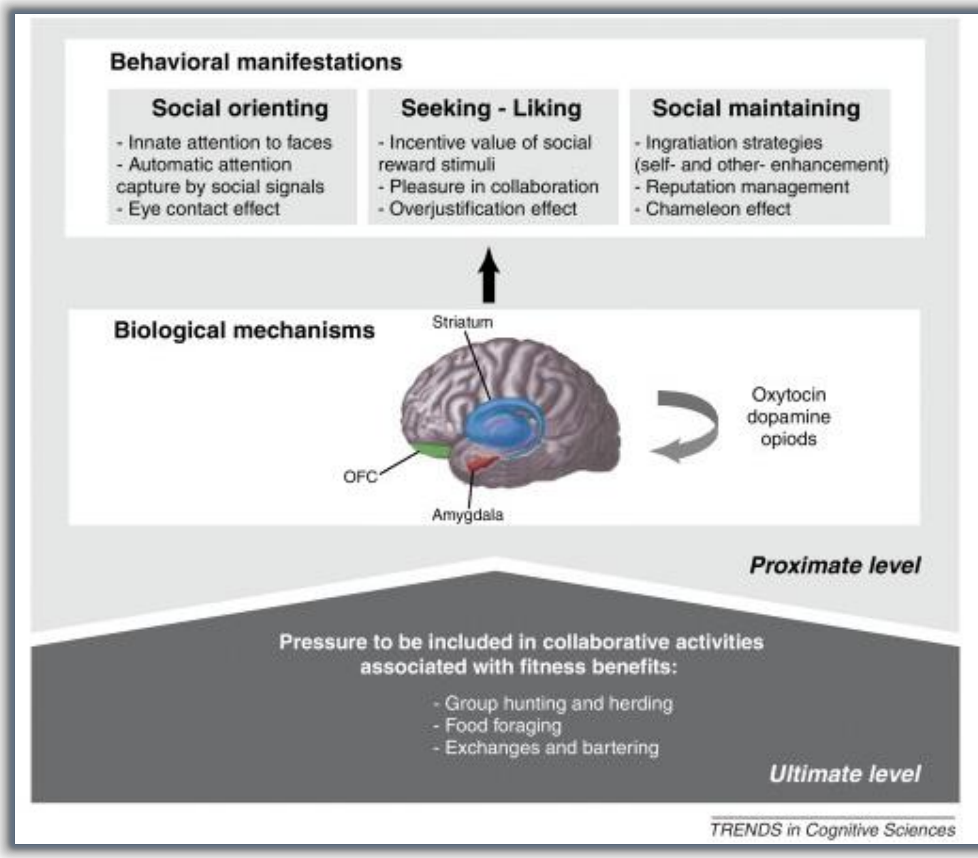

Figure 5 - Social motivation theory diagram (Chevallier et al., 2012)

connectedness. According to the social motivation theory, individuals on the spectrum exhibit a reduced tendency for social orientation, leading to fewer social experiences and, consequently, negatively impacting their learning particularly during childhood when observing and imitating others is crucial for development. This lack of social experiences contributes to atypical early brain development, which is further exacerbated by continued exposure to non-social stimuli. The theory suggests that addressing these deficits in social motivation may be the key to understanding and developing effective interventions for individuals with ASD. The authors link reduced attention to social stimuli to biological disruptions of the orbitofrontal-striatal-amygdala circuitry frequently reported in ASD (Bachevalier & Loveland, 2006; Baron-Cohen et al., n.d.) and dysregulation of certain neuropeptides and neurotransmitters. Numerous studies support this theory, demonstrating reduced attention to social stimuli in individuals with ASD (see section 1.2 for more details about social attention and autism), and it has formed the basis for many early intervention concepts. This theory has garnered significant attention and can be considered the foundational premise of the present thesis. However, the social motivation theory is not without counterevidence. It implies that reduced social attention in ASD individuals precedes other symptoms. Yet, despite social orientation deficits being observed extremely early in development from prospective studies (which follow at-risk children; E. J. H. Jones et al., 2016), non-social symptoms (e.g., related to basic attentional deficits) are already observed by six months and seem to emerge concurrently (Elsabbagh et al., 2012, 2013; Flanagan et al., 2012). It is therefore challenging to determine which symptoms appear first. Moreover, it is important to note that even in studies fully supporting the social motivation theory, numerous children with ASD exhibit preserved social attention (Pierce et al., 2016).

Another worth mentioning theory lies in the "Predictive Impairment in Autism" (PIA, Cannon et al., 2021; Sinha et al., 2014) embedded in the framework of predictive coding. Predictive coding suggests that our brain processes information by making predictions based on prior knowledge, then tests these hypotheses, and corrects these predictions (if errors) based on incoming data (Rao & Ballard, 1999). This process forms the basis of perception, attention, and learning. This theory has gained significant interest over recent years, and many hypotheses have emerged from this line of thought. For example, one hypothesis is the "hypo-prior" hypothesis, which posits that individuals with autism have weaker or less precise prior expectations (Pellicano & Burr, 2012). Another hypothesis within the predictive coding framework is the "impaired hierarchical predictive processing" hypothesis, suggesting that individuals with autism have difficulties in the hierarchical organization of predictions across different levels of processing (Friston et al., 2013). In addition to these hypotheses, the "High, inflexible precision on prediction in Autism" (HIPPEA) hypothesis has been proposed, which suggests that individuals with autism have a heightened response to predictive errors due to a very low threshold for prediction violations (Todorova et al., 2021; Van de Cruys et al., 2014). This inflexible degree of intolerance leads to numerous prediction errors making people unable to effectively learn from social situations, for example. These various hypotheses could contribute to the diverse range of challenges experienced by people with ASD, such as difficulties in understanding and adapting to new or complex social situations, perceiving, and interpreting complex social cues, and understanding the intentions of others.

### *1.1.5 Current interventions and challenge*

Providing an overview of various autism interventions is a daunting task. One of the challenges lies in the complex classification of these interventions, with many claiming to belong to clusters or even superclusters, resulting in a tangled web of categorization. However, one aspect that has gained nearly universal consensus in recent years is that interventions should be both early and intensive. Numerous studies have demonstrated that younger children who receive interventions early on make more significant progress. Consequently, there is a growing body of literature advocating for ultra-early interventions, sometimes even before the emergence of symptoms, particularly in children at high risk of developing ASD. Likewise, intensity has become a well-established principle within autism interventions (D'Elia et al., 2014; Granpeesheh et al., 2009). An intervention must be relatively intense in order to have an effect and to be generalizable, which is a real challenge in the context of ASD (Carruthers et al., 2020; Lord et al., 2006). It is worth noting that the question of intensity has been and continues to be debated. Some argue that it may be more beneficial to tailor intensity to each child's needs rather than applying a uniformly intensive approach for everyone (Hampton & Kaiser, 2016). In the literature, interventions that meet both early and intensive criteria are commonly referred to as Early Intensive Interventions (EIs).

Beyond these basic tenets and although they are relatively intertwined, two major schools constitute the autism intervention landscape. The first encompasses interventions primarily based on Applied Behavior Analysis (ABA) principles. As the name suggests, these interventions rely heavily on behavioral principles, such as positive and negative reinforcements derived from Pavlovian studies, for example. These interventions emerged early on but gained widespread popularity thanks to a study by Lovaas (1987). In his study, Lovaas presented results from an intensive (40 hours per week) ABA intervention compared to a control group of children, who still received a significant amount of intervention. In the intensive treatment group, nearly half (47%) of the children were later integrated into neurotypical public schools, achieving "*normal intellectual and educational functioning*" compared to only 2% meeting the same criteria in the control group. Interventions based on these behavioral principles then proliferated, and delivering an intervention in an intensive manner became the norm. Although they still constitute the majority of interventions today, this type of intervention, now more commonly known as Discrete Trial Training (DTT, T. Smith, 2001), has faced substantial criticism over time. These criticisms include the use of negative reinforcement and the somewhat "cold" and dehumanizing aspect of the method (Sandoval-Norton et al., 2019). To some extent, these interventions have gradually been phased out, and new interventions have emerged. Of course, these new interventions still incorporate effective elements of DTT, such as positive reinforcement, but they prioritize developmental principles in their foundations.

These interventions are regrouped under the term of Naturalistic Developmental Behavioral Interventions (NDBI, Schreibman et al., 2015). All interventions categorized under the NDBI umbrella exhibit similar traits and constituents, drawing from both behavioral and developmental theories. While NDBIs adhere to the behavioral principle of positive reinforcement, they also take into consideration personal preferences, opinions, motivations, and social relationships. The common components of all NDBIs involve implementing interventions in natural environments, sharing control between the child and the teaching partner, utilizing natural contingencies, and using behavioral strategies to teach age-appropriate skills. They also advocate for customized treatment objectives, with teaching sessions initiated by the child based on his/her motivation and may involve adult imitation of the child. Although some of these aspects can be present in modern, progressive forms of DTT, these naturalistic components are the explicit procedural components of NDBIs. Examples of NDBI interventions include Pivotal Response Treatment (PRT, Koegel et al., 1999), the Early Start Denver Model (ESDM, Rogers & Dawson, 2010), Joint Attention, Symbolic Play, Engagement, and Regulation (JASPER Kaale et al., 2012), Social Communication/Emotional Regulation/Transactional Support (SCERTS; Prizant et al., 2003). Over the years, NDBIs have emerged as promising and effective interventions to promote the development of language or cognitive skills (Frost et al., 2020; Tiede & Walton, 2019).

This thesis project includes several studies investigating children following an ESDM-based program provided in Geneva. ESDM, designed by Sally Rogers and Geraldine Dawson (2010) truly embraces the core concept of NDBI intervention. It utilizes teaching strategies that focus on interpersonal exchange, shared engagement, and communication, while also using operant conditioning, shaping, and chaining. ESDM emphasizes the promotion of language and interaction through positive interaction initiated and based on the child's motivation. It includes a "curriculum" tailored to each child's individual needs, addressing all developmental domains. The curriculum objectives prioritize teaching objectives chosen by the parents themselves. Indeed, ESDM places parents as active participants in their child's intervention by teaching them basic strategies and asking them to use them during everyday activities. In their randomized controlled trial, Dawson et al, (2010) demonstrated significant progress for children in the ESDM intervention group compared to the control group, who received treatment available in the community, over a 2-year period. Altogether, children in the ESDM intervention group increased their cognitive scores by more than 15 points, maintained their adaptive skills growth, while children in the control group increased their delay and did not experience any decrease in autistic symptom severity. A less intensive version (one hour per week), with a shorter duration (12 weeks), and provided by parents instead of a certified psychologist was tested but did not yield such positive results (Rogers et al., 2012). Indeed, both the intervention and control group children did not show significant progress or between-group differences by the end of the 12-week intervention. However, this study underscored once again the importance of early diagnosis by evidencing strong correlations between age at diagnosis and the gains observed in children. It also reflects the deep commitment of ESDM creators to place parents at the core of the intervention.

While this model has proven very efficient, in its 2-years/intensive form in the US, it is, like all the interventions subject to heterogeneous response. Indeed, while clinicians and researchers have developed numerous interventions over time, we still struggle to understand why some children exhibit rapid changes in response to an intervention, whereas other children do not to seem to experience any apparent benefits from the very same intervention. Understanding the heterogeneity in response to autism interventions is a critical and pressing issue (Vivanti et al., 2014). To address this vital challenge and tailor interventions more effectively, researchers have been tirelessly investigating several key predictors of outcome, including age, intensity of intervention, cognitive skills at baseline, social attention, parental involvement, genetic factors, and language abilities (Harris & Handleman, 2000; Tiura et al., 2017; Toth et al., 2006; Vivanti et al., 2014).

As previously stated, early onset of interventions has emerged as a powerful predictor, with a younger starting age leading to remarkable improvements in cognitive, language, and adaptive functioning (Dawson, 2008; Dawson et al., 2010; Fuentes et al., 2021; Granpeesheh et al., 2009; Harris & Handleman, 2000; Schreibman et al., 2015; Zwaigenbaum et al., 2015). Intensity of interventions is another crucial factor, with higher intensity often translating to better outcomes, though individual needs must be carefully considered (D'Elia et al., 2014; Granpeesheh et al., 2009; Hampton & Kaiser, 2016). Additionally, children who begin interventions with stronger cognitive and language skills tend to experience more significant progress across various developmental domains (Howlin et al., 2009; Zwaigenbaum et al., 2015). The role of parental involvement has emerged as indispensable in many intervention programs, with active participation and training resulting in transformative gains in children's development (Rogers et al., 2012; Zwaigenbaum et al., 2015). Cutting-edge research also indicates that genetic factors may play a crucial role in shaping treatment response, with specific genetic variations being associated with more favorable outcomes (Szatmari et al., 2016). Although significant strides have been made in identifying predictors of treatment outcomes, further research is urgently needed to refine our understanding of these factors with the pursuit of this knowledge holding the promise of better personalized interventions, ultimately improving treatment outcomes, and transforming the lives of individuals with ASD.

# First section summary

Autism Spectrum Disorders (ASD) are a group of neurodevelopmental characterized by language impairments, deficits in social interactions, and the presence of restricted and stereotyped behaviors. Over time, our understanding of ASD etiology has expanded. Currently, we know that these disorders arise from complex interactions between genetic and environmental factors. However, our comprehension of the mechanisms underlying these gene-environment interactions remain elusive and warrant further investigation. Since the initial descriptions of autism in the 1940s, the conceptualization of autistic disorders has evolved significantly through research. The perception of autism has shifted from a monolithic diagnostic entity to a spectrum encompassing multiple clinical presentations. This evolution has been reflected in the development of theories, which initially sought to explain individual symptoms but now strive to provide a broader understanding of the phenomena observed across the spectrum. Overall, research has led to substantial improvements in diagnosis and the development of effective early intensive interventions, such as the Early Start Denver Model (ESDM). Despite these advancements, there remains a critical need for a better understanding of autism's heterogeneity. As highlighted throughout this section, autism is an incredibly diverse disorder with as many clinical presentations as there are individuals. Understanding this heterogeneity represents a significant challenge in the autism field, as the multitude of manifestations complicates our ability to comprehend its origins, intervene effectively, model the functioning, or even predict progress of individuals with ASD.

## 1.2 Eye-tracking

Eye-tracking is an ideal tool for autism research. Easy to use and enjoyable for children, it allows an exploration of underlying attentional processes through the lens of visual exploration. Over the years, it has been widely used in the field and has contributed to numerous significant discoveries. In this section, we will briefly review the history of this technology, which has now become an integral part of our everyday lives. We will also discuss innovative paradigms that have emerged in recent years, which respond to the user's gaze, and the therapeutic opportunities they provide. But before delving into the details of eye-tracking and its evolution over time, it might be helpful to examine the anatomy of the eye and its visual pathways.

### 1.2.1 Eye anatomy and visual pathways

The human visual system is an intricate and efficient mechanism, much like a camera, with modern cameras being inspired by the eye's structure and function. The eye consists of a lens, a photosensitive region, and an aperture that controls the intensity of light by opening and closing (see Fig.6). So how exactly does the process of seeing something occur? When we see an image, our eye regulates the amount of light through the pupil's diameter, and the cornea and lens focus this light on the retina, creating an inverted image (N. Wade & Tatler, 2005). A small structure in the center of the retina, the fovea centralis, contains a high concentration of cone photoreceptors responsible for detailed and color vision. The light falling on the fovea forms the center of the visual field, providing a high level of detail due to the dense concentration of photoreceptors in this 1.5mm diameter region. This foveal visual field, typically representing between 1° and 2° of visual angle, contains the most detailed image within our visual field. Since the fovea region is so small, our eyes must move around and fixate on the object we want to examine, placing it right in the center of the foveal visual field for the highest accuracy and precision. Outside the fovea is the parafovea, where information is still gathered but with rapidly diminishing accuracy compared to the fovea region. Beyond this lies the peripheral visual field, which detects only low-frequency visual information.

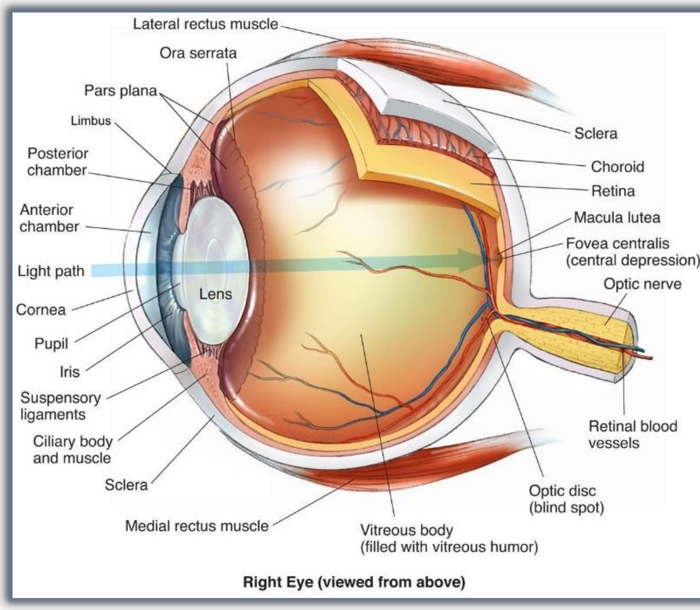


**Figure 6** - Anatomy of the eye viewed from above

Once our eyes fixate on an object of interest, the visual information begins to travel through the optic nerves to the optic chiasm, where information from the left and right visual hemifields is separated. The left visual hemifield is directed to the right brain hemisphere and vice versa. The information then passes through the lateral geniculate nucleus and suprachiasmatic nucleus of the thalamus via the optic tract before being transmitted to the left and right primary visual cortex within the occipital region of the brain (see Fig.7). Finally, the visual information is assembled and sent to other brain regions for interpretation.

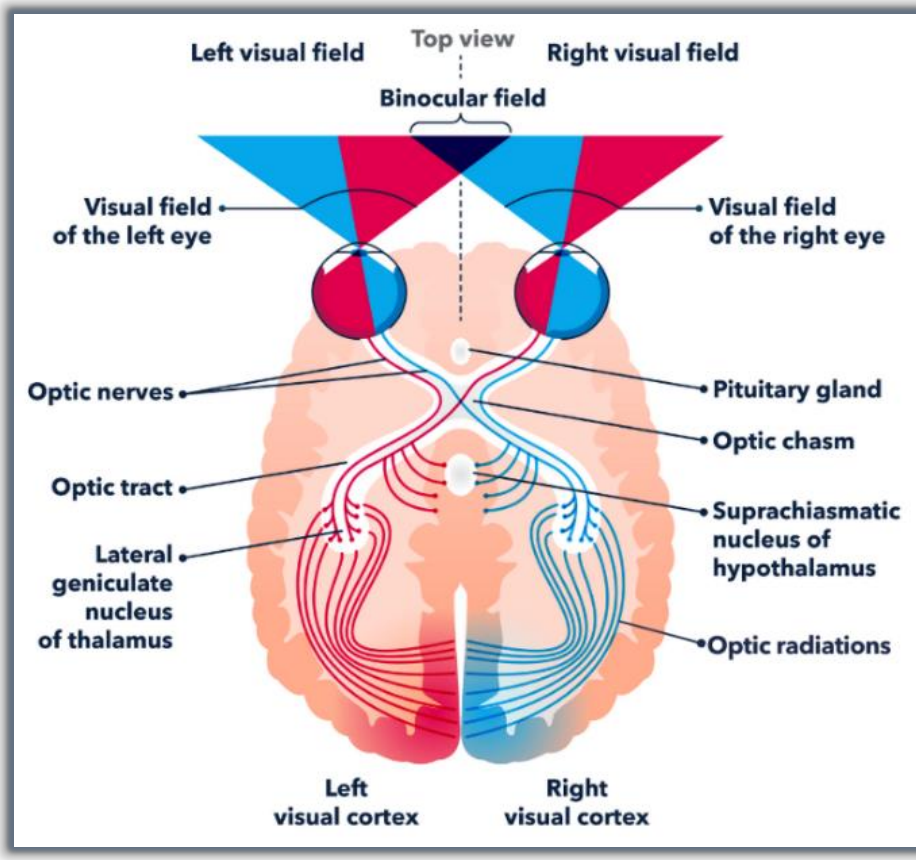


Figure 7 – Visual information pathway

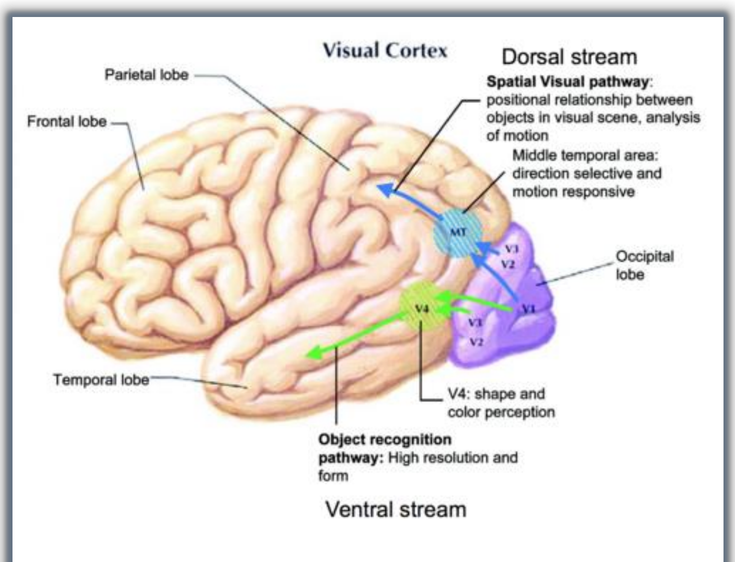


Figure 8 – Dorsal and ventral visual pathways

After reaching the visual cortex and undergoing pre-processing, the information is sent through two distinct pathways: the ventral and dorsal pathways (Mishkin et al., 1983; see Fig.8). The ventral pathway, often referred to as the "what" pathway, identifies the object's nature and assigns it a label. It projects to the temporal cortex via the occipitotemporal cortex and extends to the ventrolateral prefrontal cortex (VLPFC; Bi et al., 2016; Bracci et al., 2017; Fan et al., 2021; Kravitz et al., 2013; Mishkin et al., 1983). The dorsal pathway, often referred to as the "where" pathway, locates the object in relation to space. This pathway projects to the parietal cortex, specifically the occipitoparietal cortex, and extends to the dorsolateral prefrontal cortex (DLPFC/area; Ayzenberg & Behrmann, 2022; Freud et al., 2016; Gallivan & Goodale, 2018; Mishkin et al., 1983).

In summary, the human visual system is a complex and efficient mechanism, functioning similarly to a camera. Our eyes detect light, focus on specific objects, and transmit visual information through a series of pathways to be processed and interpreted by the brain. This intricate system allows us to perceive and understand the world around us.

### 1.2.2 Eye movements and visual attention

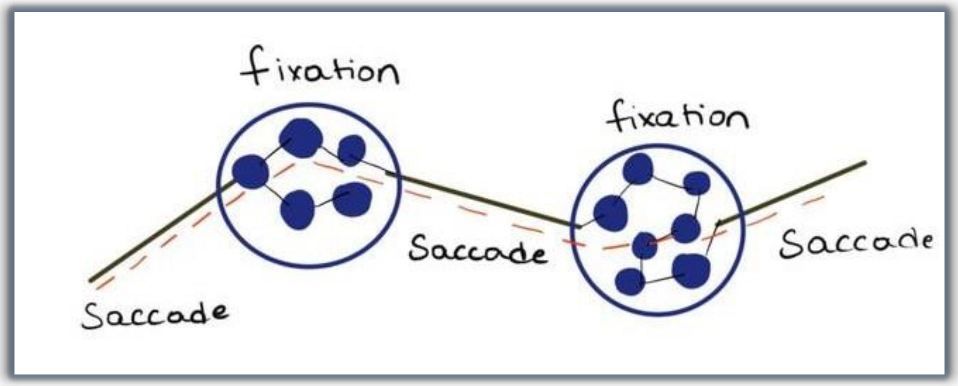


**Figure 9** – Simplistic view of saccades and fixations. Green line represents the movement, blue dots represent fixations induced by microsaccades, merged into a bigger fixation (blue circle)

Over the years, researchers have described different eye movements that serve various purposes. The two main movements of our eyes are called saccades and fixations (see Fig.9). A fixation lasts about 200 to 300ms on average and is defined as an instance of relative ocular stability that serves in the processing of visual information. The structure of our visual system positions the fovea, a central part of the retina responsible for acute and detailed vision, to capture subtle details of a scene during these periods of stability. It is within these periods of fixation that the brain harnesses the opportunity to process gathered visual information, thereby enabling the formation of a coherent perception of our environment.

Numerous empirical studies leveraging eye-tracking technology have emphasized the significance of eye fixations. Yarbus (1967) utilized an eye tracker to record participants' eye movements as they viewed a sequence of images (see Fig.10). His results suggested that fixation patterns were not random but were instead influenced by the task at hand. To achieve this, the author analyzed gaze patterns of his participants under various conditions. In one of these, he instructed participants to determine the ages of the individuals (see Fig.10 c). In this condition, fixations were mainly concentrated on the faces of individuals in the scene, evidencing the visual attention required to estimate ages. In another condition, Yarbus asked participants to recall the arrangement of people and objects in the room (see Fig.10 f) which resulted in more dispersed fixations across the entire scene. Yarbus' work was among the first to illuminate the critical role that fixations play in visual attention and how they reflect goal directed cognitive processes. Following this groundbreaking study, later research has probed further into the relationship between fixations and the cognitive processes of attention that underpin them. By the late 20th century, the scientific community had broadly embraced the idea that fixations truly reflect moment-to-moment cognitive processes. This notion has been demonstrated numerous times, with notable insights coming from reading-centered studies. For instance, studies reported that readers display prolonged visual fixations when they come across infrequent or lengthy words (Just & Carpenter, 1980; Rayner, 1998). These findings underscore the idea that visual fixations indeed serve as critical indicators of visual attention. By observing these fixations, we can gain valuable insights into the underlying cognitive processes, particularly how they adapt and respond to varying degrees of complexity in visual information.

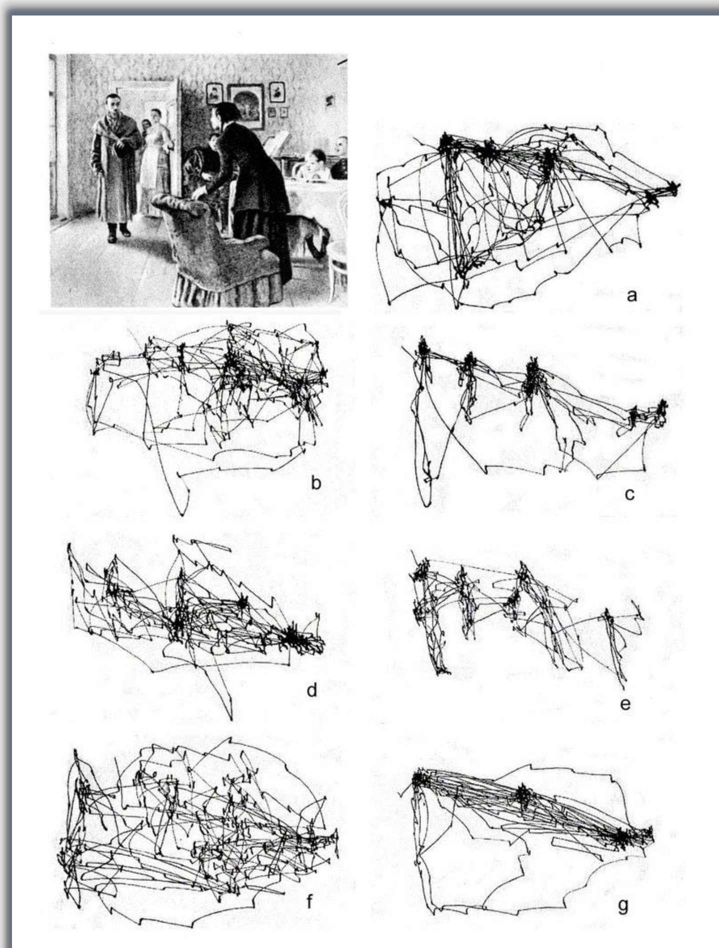


Figure 10 – Visual scan paths under different conditions (Yarbus, 1967). **a)** During free viewing **b)** Asked to estimate the material circumstances of the family **c)** Determine the ages of the individuals **d)** Guess the family's activity prior to the arrival of an 'unexpected visitor' **e)** Memorize the individuals' attire **f)** Remember the arrangement of people and objects in the room **g)** Estimate the duration of the 'unexpected visitor's' absence from the family

To benefit from the highest acuity of our fovea, we move our eyes to position the target at the center of this region. These movements are called saccades and are an indispensable mechanism in our visual exploration. During ocular saccades, our eyes move at high velocity (up to 500° per second). This movement is typically characterized by an increasing speed velocity, usually until half of the movement, followed by a decrease in velocity to stabilize the eye on the target. This velocity is entirely dependent on the distance the eye must cross to focus on the target. It is worth noting that these saccadic movements typically arise from the synergy of bottom-up and top-down influences—the former predominantly controlled by visual saliency, and the latter navigated by our personal objectives and predictions.

Among the wealth of research conducted on saccades, a study conducted by Peiyuan & Kowler (1992), shed light on the role of saccades in the perception of texture patterns. In their experiments, observers used saccadic eye movements to scan the display, comparing these observations to when the line of sight was maintained at the display center without saccades. They discovered that saccades significantly improved the discriminability of certain visual elements, specifically those in textures that did not readily segregate into target and background regions. The study suggested that the use of saccades was more beneficial than directing the eye elsewhere, reinforcing the concept that saccadic eye movements play a crucial role in overcoming lateral interference and enhancing our visual discrimination capabilities. This groundbreaking work emphasized that the perception of intricate textures is most effective when undertaken through sequences of saccades rather than mere attention shifts. Later, an interesting investigation into the cognitive mechanisms guiding saccades was undertaken by Kowler et al. (1995). They discovered that the patterns of saccadic movements were not merely dictated by a scene's visual properties. Instead, factors such as an observer's familiarity with the scene, their anticipations, and their current task objectives had significant influence over the saccadic patterns. The research revealed the indispensable role of perceptual attention in fine-tuning saccadic programming. Interestingly, their analysis unveiled a limit on the attentional demands of saccades, showing that attention could be partially diverted from the saccadic target without jeopardizing the saccade's speed or accuracy. The insights gleaned from this pioneering study underscore the vital role of cognitive factors in steering our visual focus and further our understanding of the intricate relationship between visual attention, saccades, and cognitive processing. Expanding on these findings, Land & Hayhoe (2001), transported this investigation into a more naturalistic environment by studying participants' eye movements while performing everyday tasks such as making tea or sandwiches. The study compellingly demonstrated once more that saccadic targets were not randomly selected. Instead, visual attention often preempted the saccadic movement, implying a sequence where attention shifts preceded eye movements. This finding resonates with the overt and covert attention principles (Posner, 1980) with the former involving eye movements toward an object of interest and the latter representing mental focus on an object without direct visual engagement. Within this paradigm, saccades are viewed as an embodiment of overt attention, closely aligned with our perceptual focus. Land & Hayhoes' results reaffirmed that saccades extend beyond mere instinctual responses to visual stimuli and are intricately orchestrated by our attention focus, playing a pivotal role in guiding our visual attention. Overall, all studies pointed out that saccades emerge not just as physiological responses, but as sophisticated mechanisms deeply embedded within our cognitive processes, attention, and anticipatory responses.

Eye-tracking research has greatly deepened our understanding of the visual system, revealing that our eyes are capable of a sophisticated type of movement known as "smooth pursuit." Unlike the abrupt shifts seen in saccades, smooth pursuit is a refined, continuous motion allowing us to maintain focus on moving objects, vital for diverse tasks such as catching a flying ball or attentively observing wildlife.

However, the value of smooth pursuit extends far beyond keeping objects within our line of sight. According to a study by Kowler et al. (2019), smooth pursuits are also not a reactive response to sensory input. Instead, these movements can anticipate changes in motion paths, acting as a safeguard against any potential disruptions from sensorimotor processing delays. The predictive nature of smooth pursuit movements is one of their most fascinating aspects. These movements can be triggered by perceptual cues or memories of recent motion, demonstrating a cognitive dimension that goes beyond immediate sensory motion. Even when a target is occluded, or hidden, the pursuit continues, and its accuracy is further enhanced when dealing with self-generated or biologically realistic target motions. In this light, retinal motion becomes one piece of a larger puzzle, contributing alongside various other cues to shape the predictive responses inherent in smooth pursuit movements. This intimate connection between smooth pursuit and cognitive processes also extends to the realm of attention. While smooth pursuit can occur independently of attentional shifts, studies such as those by Khurana & Kowler, (1987) and Lovejoy et al., (2009) have shown that when attention is dedicated to the moving target, the quality of smooth pursuit eye movements is noticeably improved. This interplay paints a complex, yet intriguing picture of our visual system where attention and smooth pursuit movements, despite their capacity to operate independently, are intricately interconnected. It underlines that attention does more than just kick-start smooth pursuit movements, it significantly enhances them, thereby optimizing our visual system's effectiveness.

In conclusion, eye movements, be it fixations, saccades, or smooth pursuits, serve pivotal roles in visual attention, underpinning how we perceive and interact with our surroundings. These movements extend beyond physiological responses and are deeply interwoven with our cognitive processes, task goals, and anticipatory responses. Moreover, the attention not only triggers these movements but significantly influences their quality and efficacy, thereby shaping our visual perception of the world.

Despite the longstanding knowledge of fixations and saccades in eye movement research, reaching a consensus on their accurate classification remains an ongoing challenge. The literature presents various methods, each with their strengths and limitations, which complicates the establishment of a universally agreed-upon approach (Andersson et al., 2017). Dispersion-based methods focus on the spatial distribution of fixation points. They classify fixations as clusters of points with spatial dispersion below a predefined threshold, as suggested by Salvucci & Goldberg, (2000). Although this method is simple and intuitive, it may not perform well when there is significant variability in fixation durations or if the data is noisy. Duration-based methods rely on the fixation duration to distinguish between fixations as periods of stable gaze and saccades as rapid movements between these stable periods (Blignaut, 2009). This approach is less sensitive to noise, but it can be challenging to determine the appropriate duration threshold for various tasks and populations. Velocity-based methods utilize eye movement velocity to identify saccades and fixations, with saccades representing rapid eye movements and fixations corresponding to periods of low velocity (Nyström & Holmqvist, 2010). These methods are popular because they can adapt well to variations in eye-tracking data quality and are robust to noise. Tobii, one of the main leading eye-tracking company, employs a velocity-based method called the "I-VT Filter" (Identification by Velocity Threshold; Olsen, 2012) as its default classification algorithm. Dual-threshold methods combine duration and dispersion approaches, using thresholds for both fixation duration and spatial dispersion (Komogortsev & Karpov, 2013). These methods aim to overcome the limitations of individual threshold-based methods, but they require careful tuning of multiple parameters. Recent advancements in eye-tracking research have incorporated machine learning and clustering algorithms to identify fixations and saccades based on eye-tracking data features (Zemblys et al., 2018). These methods have the potential to improve classification accuracy and adapt to individual differences, but they may be more computationally demanding and require larger datasets for training. In conclusion, the choice of classification method often depends on the research objectives and data characteristics. While no single method has emerged as the definitive approach, the continued development and evaluation of new techniques will help to advance our understanding of eye movements and their role in perception and cognition.

### *1.2.3 Definition and historical aspects of eye-tracking*

Numerous sources indicate that the origins of modern eye movement research can be traced back to the 19th century (Płużyczka, 2018; N. J. Wade, 2010; N. Wade & Tatler, 2005). It was during this era that French ophthalmologist L.E. Javal and his associate M. Lamare made groundbreaking observations on eye movements during the reading process, noting that some words were not fixated (Javal, 1878; Lamare, 1892). This discovery sparked interest in understanding the complex dynamics of human eye movements. In 1908, Huey developed what is now considered as the first eye-tracking device, featuring a contact lens equipped with aluminum pointers to monitor shifts in gaze direction. Despite being notoriously uncomfortable and necessitating the use of cocaine to alleviate participant discomfort, this innovation marked a significant breakthrough in the field of eye movement research. Approximately three decades later, the first non-invasive eye-tracker was introduced by Buswell (see Fig.11). Employing light beams reflected on the cornea and captured on film, Buswell demonstrated that eye movements during reading varied according to age and reading proficiency (Buswell, 1937). This pioneering work laid the foundation for the subsequent development of eye-trackers that focused on increasing mobility, ease of use, and accuracy.

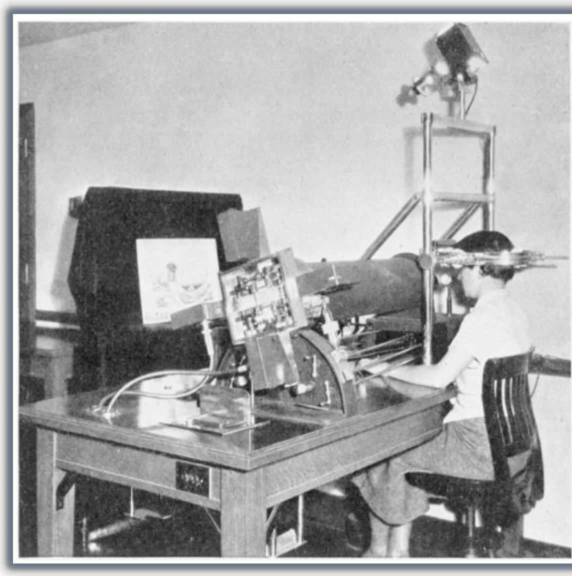

**Figure 11** – Photography of Buswell's eye-tracker in 1937

A major advancement in eye movement research emerged in the 1960s, when Russian scientist Yarbus, already mentioned, devised an eye-tracker that employed a rubber suction cup and mirror attached directly to the human eye's sclera. Despite the discomfort involved in this procedure, Yarbus was the first to establish a clear link between eye movements and a participant's objective, revealing that individuals exhibit logical patterns when viewing specific stimuli (Yarbus, 1967; see Fig.10). This finding significantly expanded the understanding of the cognitive processes underlying eye movements and paved the way for further research in the field. From the 1970s onwards, eye-tracking technology experienced rapid evolution, with the advent of devices compatible with laboratory computers. Eye-trackers became increasingly accessible, efficient, and mobile (Rayner, 1998), paving the way for widespread adoption across numerous fields, including neuroscience, psychology, marketing, industry, aviation, or even maritime risk management (Martinez-Marquez et al., 2021).


Figure 12 – Eye-tracking device (Tobii Eye-Tracker 5)

Contemporary eye-trackers typically comprise a device positioned beneath a screen, equipped with sensors to detect where an individual is looking (see Fig.12). These devices emit infrared rays that reflect off the eye, and algorithms then analyze the reflections to estimate gaze position on the screen. This technology is now unobtrusive, non-invasive, and painless, making it ideal for a wide range of applications. Eye-tracking has become an integral part of our lives since the 2000s, with devices often integrated into computers and gaming systems, offering post-game replays to enhance performance. Researchers have also employed eye-tracking to study user interactions with websites and to optimize web design. In the field of marketing, eye-tracking has been used to evaluate the effectiveness of advertisements and product packaging designs. Wearable eye-trackers are gaining popularity, frequently incorporated into virtual reality headsets. These devices enable researchers to study how users interact with virtual environments, and developers to create more immersive and realistic experiences. Eye-tracking technology has also been utilized in medical research, for example, to study visual impairments, diagnose neurological disorders, and assess cognitive function. The implementation of eye-tracking in everyday technologies, such as automobiles, indicates that the field will continue to advance for years to come. Current research includes developing systems to monitor driver fatigue and distraction, as well as enhancing vehicle safety features. As eye-tracking technology continues to evolve, it is likely to play an increasingly vital role in understanding human behavior and improving human-machine interactions.

As the Internet of Things (IoT) continues to grow, it is likely that eye-tracking will be integrated into a wider array of devices and applications. As technology continues to evolve, it is likely that eye-tracking will play an increasingly vital role in understanding human behavior and improving human-machine interactions across various domains.

## 1.2.4 Novel paradigms in eye-tracking: Gaze-contingency

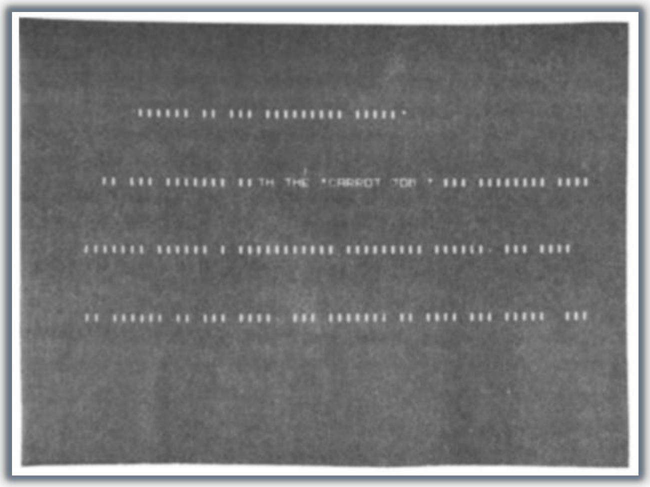

Figure 13 – Photography of one of the first moving window gaze-contingent paradigm (Reder, 1973)

As mentioned throughout this section, the primary purpose of eye-tracking is to record eye movements to study how humans observe a particular stimulus. Initially designed as a passive recording tool, researchers have since imagined more interactive ways to use this technology. For example, studies investigating reading mechanisms have attempted to make text appear in the foveal field of vision while blocking the appearance of letters in the periphery. This approach allows researchers to follow the reading path (McConkie et al., 1978; Reder, 1973; see Fig.13). These paradigms are referred to as "gaze-contingent".

Although it may seem like a recent development, gaze-contingent paradigms emerged as early as the '70s, thanks to advancements in computer technology. These innovative paradigms enable users to receive immediate feedback on their visual exploration. The stimuli presented are now interactive with the user's gaze, and the experience uses the person's gaze as a trigger. In the early years, gaze-contingent paradigms were primarily moving window paradigms, where only the foveal field of view is visible to the participant, and the rest of the visual field is masked. These interactive paradigms were initially used to investigate basic ocular phenomena such as the extent of the perceptual span (McConkie et al., 1978; Pomplun et al., 2001) or the saccadic adaptation (Garaas et al., 2008) for instance. Later, the processes explored through gaze-contingent paradigms became more complex and diverse. Today, gaze-contingency is implemented in studies investigating face exploration (Keemink et al., 2019; Wang et al., 2019) or measuring the rewarding value of interaction in toddlers with ASD (Vernetti et al., 2018) for example.

Eye-tracking and its contingent paradigms have quickly become augmentative and alternative communication (AAC) tools for people with reduced mobility and speech limitations, such as those with neurodegenerative diseases (Light & McNaughton, 2014; Maresca et al., 2019). Test batteries have been developed to assess cognitive skills, previously untestable, in individuals who can no longer communicate verbally or move (Poletti et al., 2017, 2018). Additionally, many companies have developed eye-trackers and applications allowing these people to communicate with others through voice synthesis coupled with the eye-tracker's gaze-contingency, significantly improving their quality of life (Elliott et al., 2022; Spataro et al., 2014; Vessoyan et al., 2018). Eye-tracking as an AAC tool is a prime example of a more therapeutic use of gaze-contingency and eye-tracking overall. This new application has gradually become more widespread, and researchers have been working to develop gaze-contingent remediation paradigms.

A recent review by Carelli et al., (2022) highlighted the current scarcity of eye-tracking applications as remediation or training tools. They reported a total of only 21 studies using gaze-contingency technology for this purpose, with 8 of these studies including only healthy subjects. One example of a very interesting study using gaze-contingency as a remediation tool is the one by Lazarov et al., (2017). The authors asked 40 adult participants to select their preferred music as a positive reinforcer. They then presented face arrays containing neutral faces and others with negative expressions. In the intervention, the chosen music played whenever the participant looked at a neutral face. In the control group, the music played constantly in the background, regardless of the participant's gaze direction. The intervention spanned four weeks, with two 20-minute sessions per week. Participants in the gaze-contingent condition experienced a significant increase in time spent looking at neutral faces and a corresponding decrease in anxiety symptoms. In contrast, the control group saw no symptom improvement and no change in time spent gazing at neutral and emotional faces. This experiment highlights the therapeutic potential of gaze-contingent paradigms in eye-tracking. Yet, as it is our main concern here, there is currently only one study aimed at intervening in ASD. This study by Wang et al., (2020) used gaze-contingency to reorient the gaze of children with ASD towards regions typically observed during a movie of an actress (see Fig.14). These regions were extracted from the replay of 41 typically developing (TD) children who had previously viewed the same movie. Children with ASD were split into two groups: one with gaze-contingent cues (n=16) and another without cues (n=19). By the end of the protocol, children in the cue group had a significantly higher percentage of time spent on the face, although this was mostly driven by a decrease in time spent on faces in the other group. Results showed that the gaze-contingent cues helped mitigate the decrease in time spent on faces observed in the no-cue group. Although this study did not provide clear evidence of a potential increase in social orientation in ASD, it demonstrated the feasibility of gaze-contingent remediation in autism and highlighted the need for further studies in this area. Taken together, the current state of research using gaze-contingency in eye-tracking as a remediation tool underscores its preliminary nature. There are still many areas to explore, and I hope to contribute to these innovative studies with this thesis.

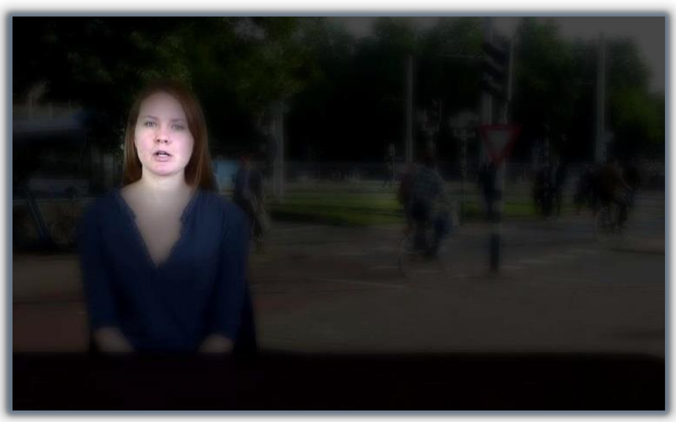

**Figure 14** – Screenshot from the gaze-contingent task used in Wang et al (2020)

# Second section summary

In this section, we overviewed the basic ocular mechanisms, and we familiarized with fixations and saccades. Saccades being the rapid ballistic eye movements that allow the gaze to move, and fixations being those moments when the eye lands on something to examine it. We have also evoked the history of eye-tracking in the main lines, beginning in the 19th century with studies about reading and then rapidly evolving towards the first eye-trackers, relatively simple and sometimes fairly barbaric using lenses and aluminum rods on it to track gaze. Technological advances have subsequently improved these eye-trackers by allowing more and more advanced research on eye movements. Today's eye-tracking systems generally work via infrared rays reflecting on the participant's cornea, allowing to detect the eyes and their direction relative to the screen. Technological progress continues today and can be seen notably with the implementation of eye-tracking in everyday objects. Today eye-tracking is used in a multitude of sectors such as neuroscience but also marketing or even sports. All this popularization led to an increased interest in developing new paradigms within literature. The “latest”, or at least the most innovant, are called gaze-contingent paradigms as they enable the presented stimuli to respond to the person's gaze. Many people foresee therapeutic potential in these new paradigms, and studies have already evidenced convincing results regarding the use of gaze-contingent paradigms as remediation tools, helping in reducing anxiety disorders for example. Within the autism field, eye-tracking have been widely used to investigate visual explorations patterns in a multitude of paradigms and led to significant discoveries. Nonetheless, the field of autism has only just begun to explore the remediation possibilities offered by gaze-contingent paradigms, far from using their full potential.

## 1.3 Social attention

As expressed in subsection 1.1.4, the "Social Motivation theory", or at least the idea that reduced social attention can be observed in some individuals with autism, is the starting point for this thesis. We will therefore tackle social attention in more details, its definition, the brain networks underpinning it, but also its role in typical development, in adults and then in ASD.

### *1.3.1 Definition and underlying networks*

Social attention is a term commonly used in autism literature, yet its definition is often unclear, and it is interchangeably used with various other concepts. The challenge of defining social attention precisely, as well as developing a unified concept, has been emphasized and discussed by Salley & Colombo (2016). The authors analyzed different definitions and interpretations that social attention has garnered within the literature and proposed an interesting framework to better conceptualize this ambiguous term. They define social attention in their framework as follows: *"[…] we suggest that current usage of the term can be distilled into three functional categories. First, social attention can be considered in terms of* behavior *directed toward coordination of attention during interaction with others (i.e., joint attention or nonverbal social communication behaviors). Second, social attention can be considered as* motivation *to engage with others, including atypical populations with possible deficits in motivation for social engagement (i.e., ASD). Third, social attention can be considered as* attention *(orienting, focusing and disengagement of visual systems) in the context of social streams of information.*". They clarify that the three functional categories of social attention are not necessarily independent and may be interrelated. I here propose to take this description as a starting point and to argue that social attention is the umbrella concept that encompasses the different functional categories mentioned by the authors: behavior, motivation, and attention. One allowing the other to develop and conversely. You may notice that during my work, I focused more on one basic part of social attention, namely social orientation, which corresponds to the preferential attention selection of social information within our environment and is closely related to motivational aspects.

Therefore, in this thesis, we will use the term social attention as this umbrella concept. Social attention is supported by a vast network of cortical areas. In 2009, Klein et al. proposed that social attention relies on three main pathways operating in conjunction with one another. One pathway is responsible for orienting/selecting information, another for rewarding information, and a third for processing social information (Klein et al., 2009; see Fig.15). Interestingly, these pathways align well with the different functional categories proposed by Salley & Colombo (2016), as there is a basic orienting process, a social processing pathway in collaboration with a reward system that contributes to increased social motivation. This, in turn, modulates social orienting throughout development, leading to the growth of complexity in social behaviors over time.

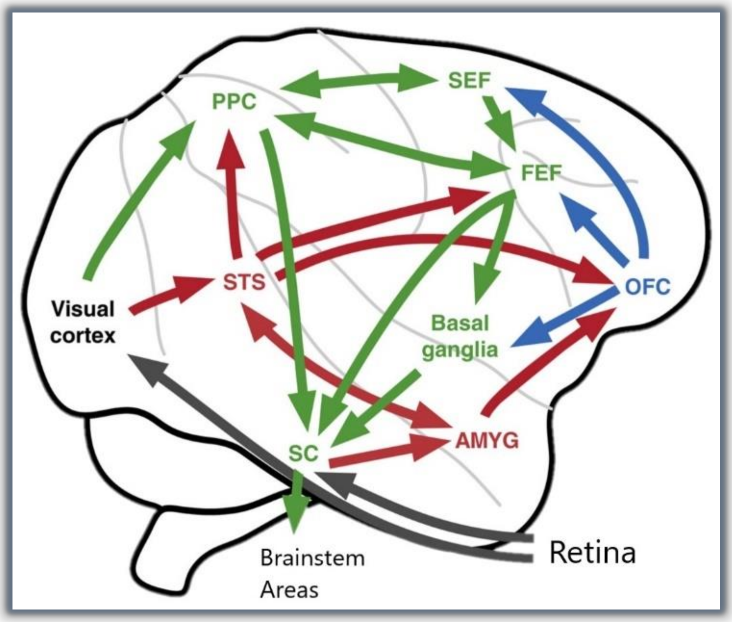


Figure 15 – Connectivity of social (red), reward (blue), and orienting (green) cortical areas underpinning social attention (Klein et al., 2012)

The orientation pathway consists of the Posterior Parietal Cortex (PPC), which is involved in processing spatial information, including the perception of objects and their locations in space. The PPC also plays a role in selective attention, enabling us to focus on essential stimuli while ignoring irrelevant ones (Heinen et al., 2017). Other structures along the orientation pathway include the Secondary Eye Fields (SEF) and Frontal Eye Fields (FEF), a pair of brain regions located in the frontal lobes that receive information about intended movements from other parts of the brain and, in turn, generate the appropriate motor commands (Heinen et al., 2014; Moore et al., 2003). Next in this pathway are the Basal Ganglia, a group of subcortical nuclei located deep within the brain, involved in regulating voluntary motor movements, procedural learning, habit formation, and reward-based learning (Qiu et al., 2009; Riva et al., 2018; Shaw et al., 2014). Finally, the orientation pathway also comprises the Superior Colliculus (SC), which receives direct input from the retina as well as other brain areas, integrating this information to generate appropriate motor responses, making it essential for orienting responses and directing the eyes, head, and sometimes the entire body toward a new stimulus (Basso et al., 2021; Moschovakis, 1996). It represents a key structure in the integration and processing of sensory information, as well as the control of eye movements and attention.

The social pathway includes two main structures: the Superior Temporal Sulcus (STS), a crucial structure for many functions in the brain, notably involved in social perception, processing of facial expressions, body language, and biological motion (Hein & Knight, 2008; Saitovitch et al., 2012; Zilbovicius et al., 2006); and the amygdala (AMYG), a vital orchestrator in every process related to emotions, ranging from basic emotion processing and emotional learning to higher cognitive decision-making (Amaral & Nordahl, 2022; Baxter & Murray, 2002; Gallagher & Chiba, 1996; Meisner et al., 2022; D. M. Smith & Torregrossa, 2021; Warlow & Berridge, 2021). The AMYG also projects to the PPC, and Orbito-Frontal Cortex (OFC), a key structure in the last pathway, the reward circuitry, which includes anticipation and experience of pleasure. The OFC is known to play a crucial role in social behaviors by helping us interpret and respond to social cues and associating/modulating rewards with information (Atmaca et al., 2018; Fariña et al., 2021; Fischi-Gomez et al., 2021).

In humans, the importance of social is such that, according to the "Social brain hypothesis" (Barton & Dunbar, 1997; Brothers, 1990; Dunbar, 2009), our brains have evolved to develop larger regions capable of processing increasingly complex social information. For many, the prioritization of social information in our environment is considered an evolutionary adaptation. This adaptation was favored through natural selection and evolutionary processes because social cooperation is essential for the survival and reproduction of the human species. The crucial role of social interactions within the evolutionary path of our brain is supported by numerous aspects. Firstly, our brain is particularly adapted to process social information, such as facial expressions, emotions, voices, body language, and behaviors of other living beings. Additionally, the brain regions involved in processing all this social information, such as the prefrontal cortex, the anterior cingulate cortex, or the superior temporal regions mentioned above, are highly developed in humans compared to other animal species (Rilling, 2014; Semendeferi et al., 2002). Finally, it is also supported by the significant impact of social interactions on the developmental course and plasticity of our brain during childhood and throughout our lives influences cognition, emotion, and behavior.

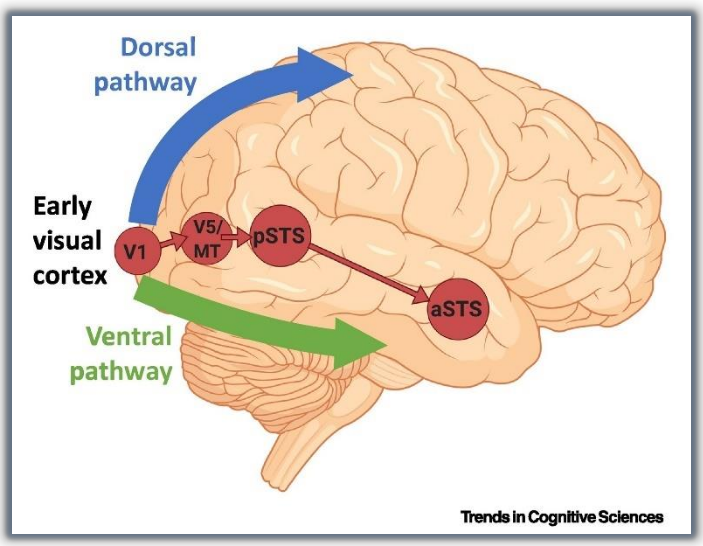

Figure 16 – Third visual pathway (Pitcher & Ungerleider, 2021)

In fact, our brains have become so specialized in processing social information that it has recently been suggested that a third visual pathway (TVP) exists, in addition to the dorsal and ventral ones, specifically for faces and social stimuli (Pitcher & Ungerleider, 2021; see Fig.16). This pathway, unsurprisingly, includes regions already discussed in the social pathway of social attention, such as the STS, a key region in this pathway. This third specialized pathway projects from the early visual cortex (V1) to motion-selective visual areas (V5/MT), to the posterior STS, and to the anterior STS. The existence of this specific pathway provides additional evidence of the importance of prioritizing these stimuli in our development. Furthermore, its autonomous activation, independent of the ventral pathway, supports the need for rapidly processing social information within our environment through specialized brain regions. However, research on the TVP must be expanded, especially since the connections described remain somewhat speculative or imprecise (Weiner & Gomez, 2021).

### *1.3.2 The importance of social attention during early infancy*

Social attention emerges very early during infancy. A groundbreaking study by Reid et al., (2017), demonstrated this by projecting face-like or inverted light points into the wombs of pregnant women using 4D ultrasound technology. They assessed over 39 fetuses in their 3$^{rd}$ trimester and found that the fetuses were more likely to turn their heads in response to upright light points compared to inverted configurations. This result suggests that the preference for faces and social stimuli does not require any postnatal experience but is rather inherent in humans. From birth, children exhibit a clear preference for faces, which has been extensively investigated through eye-tracking studies, revealing that during the first year of life, toddlers' interest in faces gradually increases (Frank et al., 2009; Simion & Giorgio, 2015; Slater et al., 1998). Notably, this preference is mainly driven by the upper facial features (Farroni et al., 2005; Turati et al., 2002) emphasizing the critical importance of the eyes in prosocial behavior from a very young age. Yet it appears that this interest is also modulated by the presentation modality over time, with an initial preference for static faces followed by an increasing preference for dynamic, moving faces. While research shows a marked and growing interest in faces during the first year of life, this trend tends to slow down or even gradually decline from the second year of life (Libertus et al., 2017). Collectively, these findings underscore the innate social orientation of humans from birth and even before and the development of the latter following postnatal experiences.

But why do we exhibit this inherent preference for social information? Studies on child development provide a comprehensive understanding of this phenomenon, emphasizing the extent to which humans are social animals. At birth, unlike many animals, human infants are entirely dependent on their environment and the people who care for them. In essence, our survival hinges on our ability to quickly communicate with and learn from our social surroundings. Throughout childhood, most of our learning occurs through observation of our social environment, making social orientation crucial during infancy, as it constitutes the very foundation of our development. By observing others and benefiting from the tremendous neural plasticity during childhood, children progressively develop more complex socio-cognitive skills, which then serve as building blocks for even more advanced abilities.

For instance, joint attention, defined as "*a goal-oriented behavior the primary of aim of which is to share experience with other people*" (Mundy et al., 2009) has been shown to be strongly predicted by early social orienting abilities (Edwards et al., 2015; Franchini et al., 2017). Schietecatte et al., (2012) demonstrated this by following 31 toddlers aged 3, 6, and 12 months, revealing that the proportion of time spent looking at the eye region during a dynamic video was predictive of joint attention abilities later on, thus highlighting a close relationship between these two core concepts of social attention during development. Joint attention is a critical skill during typical development, as shared attention facilitates greater learning, for instance, regarding the function of an object. Interestingly, the development of social joint attention behaviors during the first year of life parallels the development of brain circuits governing smooth eye-pursuit. During this period, children gradually gain control over eye movements and transition from a sticky gaze, to spastic saccadic movements to follow an object, to smooth pursuit as a result of brain maturation during this first year of life (Luna et al., 2008). The development of such eye-movement control enables increasingly complex social behaviors, such as gaze following and joint attention, as self-awareness grows.

Social orientation and attention to others are also essential when attempting to imitate someone, a critical skill for a child when learning anything. Imitation was originally defined by Thorndike, (1898) as "*learning* *to do an act from seeing it done*" emphasizing its inherent social component. Although studies on newborns suggest that imitation might be innate (Davis et al., 2021; Meltzoff & Moore, 1977), it is more likely to be built through observation of others (S. S. Jones, 2009) as a developmental ability. Imitation is thought to be primarily supported by the mirror neuron system (Iacoboni et al., 1999; Iacoboni & Dapretto, 2006) and is observed early in development, particularly in the imitation of facial expressions. Imitating facial expressions during infancy aids in the development of infants' social-emotional abilities. For example, when an adult smiles, the baby gradually associates this expression with joy or satisfaction by attempting to imitate it. Through repeated exposure and imitation, they also learn to identify the emotion and respond accordingly. Moreover, facial imitation has been linked to facial muscle development. As babies imitate facial expressions, they, in turn, develop their facial muscles, enhancing their ability to communicate with others, primarily relying on non-verbal cues at birth. After approximately 12 months, infants begin to imitate more complex actions, allowing them to acquire new skills related to autonomy (e.g., eating or dressing independently) or play, progressively incorporating deferred imitation of previously observed actions into their scenarios.

In turn, imitation and joint attention skills become particularly important in building language. Indeed, imitation is acknowledged as the starting point of communication, both verbal and non-verbal (Carpenter et al., 1998; Donald, 1991; Ingersoll & Lalonde, 2010; Sherman, 1971; Young et al., 2011). For instance, Toth et al., (2006) found a positive correlation between immediate imitation abilities and concurrent language proficiency in preschoolers with autism, while deferred imitation was associated with language development over a two-year period. Additionally, they found that joint attention skills were strong predictors of later language skills. This finding is supported by other studies pointing at a close relationship between joint attention skills and the development of subsequent language. For example, Brooks & Meltzoff, (2005) assessed 96 children at 9,10 and 11 months (32 children in each group). They observed that children with a higher propensity for following gaze at 10 and 11 months had significantly higher language skills at 18 months. This held true for both productive and receptive aspects of language. Predictions based on the child's propensity for gaze-following were even more accurate than when using the number of vocalizations as a predictor. Returning to imitation, it is noteworthy that during the first months of life, the adult serves as a model of imitation by repeatedly producing imitations of the child's vocalizations (Athari et al., 2021; Kokkinaki & Kugiumutzakis, 2000). Parental imitation of vocalizations promotes language and turn-taking by responding contingently to the child (Ishizuka & Yamamoto, 2016). This phenomenon of imitation by parents also reinforces the idea that imitation is learned through observation, as opposed to being innate.

These skills are just a few examples of key competencies for our development, but they aptly illustrate how social attention shapes us during early infancy. As we grow, the social world continues to exert a major influence on us, significantly contributing to the formation of our identity during adolescence (Collins & Gunnar, 1990; Youniss & Haynie, 1992) and the development of emotion regulation (Silvers, 2022) for example. Even later in development, social attention remains crucial during adulthood, as it enables us to maintain positive social relationships, communicate effectively with others, understand the needs and feelings of others, and successfully interact in complex social situations (Sakurai, 2022).

In conclusion, social attention is an inherent and critical aspect of human development, beginning from the prenatal stage and continuing throughout life. Our innate preference for social information shapes our growth, enabling us to acquire vital skills such as imitation, joint attention, and language. As we progress through various stages of life, the influence of the social world remains significant, playing a key role in our personal identity formation, emotional regulation, and social functioning. Understanding the importance of social attention can help inform educational practices, interventions, and support systems to foster healthy development and social well-being across the lifespan.

### *1.3.3 Social attention in autism*

In his seminal report, Leo Kanner reported "*an unusual memory for faces*" described by the father of one of the very first autistic children described. This unusual memory for faces already hinted at an atypical attention to faces in autism. Additionally, descriptions of the children as being "*withdrawn*," "*in their world*," and "*not caring about others*" later made social difficulties a core symptom of ASD, suggesting a different kind of appeal towards the social world than that observed in typical development. Over time, evidence for neurodivergent social attention in individuals with autism has accumulated. In this final subsection, we will overview the brain differences that might underly atypical social attention, as well as discuss the behavioral evidence provided by eye-tracking studies, and their implications through the lens of the "Social Motivation Theory" (Chevallier et al., (2012).

Investigations of the neuroanatomy of people with ASD have revealed both structural and functional differences in many brain regions, including those that play an important role in social attention. For instance, the fusiform face area (FFA), a brain region heavily involved in face processing, has been extensively documented in ASD (Schultz, 2005), with increased cortical thickness associated with impairments in face processing (Dziobek et al., 2010). An overall hypoactivation of the FFA in ASD is also generally reported and acknowledged (Grelotti et al., 2005). Other regions, such as the mirror neuron system, briefly discussed when addressing brain regions underpinning imitation skills, also appear to diverge in ASD. Studies have reported that their activation strength during imitation tasks appears to be negatively correlated with social symptom severity (Dapretto et al., 2006; Iacoboni & Dapretto, 2006). In addition, the superior temporal sulcus (STS) region, a key component of the social visual pathway described above, is not exempt from atypical differences. These include decreased levels of gray matter and atypical activation during social tasks, particularly eye-gaze perception tasks (Saitovitch et al., 2012; Zilbovicius et al., 2006). The amygdala, a critical region for emotion regulation, has also been found to be atypical within ASD. A study analyzing MRI data from young children found that those diagnosed with ASD had larger right and left amygdalae compared to controls, and that the degree of enlargement was positively correlated with social and communication deficits at age 5 (Schumann et al., 2009). An earlier study by the same team investigating at older children did not find these observations (Schumann et al., 2004). These divergent results have led to a current consensus that this overgrowth observed during childhood might slow down or even reverse during development, which is a similar brain developmental pattern to what is observed in frontal regions, for example. Indeed, frontal regions have also received considerable attention, particularly in the context of the theory of executive dysfunction in the autistic population. Frequently reported results describe structural differences and, in particular, greater frontal lobe volumes within autistic individuals during childhood (Crucitti et al., 2022). However, an even more frequently reported difference concerns connectivity, with many studies generally emphasizing increased local connectivity at the expense of long-distance connectivity (Catani et al., 2016; Courchesne & Pierce, 2005). This elevated local interaction, along with diminished long-range reciprocal activity and connectivity between cortical regions, would result in impaired complex, context-rich feedback, guidance, and regulation of lower-level systems (Courchesne & Pierce, 2005; Just et al., 2012). Continuing with the enumeration of potentially disrupted regions of the social attention network, basal ganglia have been investigated, particularly due to their potential importance in maintaining the repetitive behaviors observed in ASD. Studies have demonstrated increased putamen volumes (Sato et al., 2014), decreased volume of globus pallidus (Sussman et al., 2015), and increased caudate nucleus volume associated with increased RRB (Hollander et al., 2005; Rojas et al., 2006) in ASD. However, here again, volumetric differences may be age-dependent, as studies have shown greater caudate nucleus size in older patients but not in adolescents, suggesting later overgrowth in this area (Wegiel et al., 2014). Autism, being a neurodevelopmental disorder, thus encompasses a multitude of neuroanatomical differences, in addition to those briefly mentioned and focusing primarily on the regions underlying social attention. Although we are beginning to understand the functionality of different brain regions, it is still challenging to comprehend the various implications of each observed modification in the brains of individuals with ASD, given the considerable neurodiversity exhibited by this population.

Though brain alterations underlying social attention are significant, the latter has been extensively studied in people with autism at a behavioral level as well. For years, research on social attention in children with ASD has been conducted. For example, a study by Dawson et al., (1998) measured orientation towards social stimuli (name calling and hand clapping) versus non-social stimuli (shaken rattles) and shared attention abilities in young TD children compared to children with ASD. These skills were measured live in the laboratory through interactions with an examiner, without the aid of any technology. This study demonstrated that many children with ASD had difficulty orienting towards social stimuli, and among those who succeeded, they exhibited a longer disengagement time compared to TD children. Furthermore, this study revealed a close relationship between orientation towards social stimuli and shared attention skills, reinforcing the idea of an interrelated development of social attention abilities. Other studies investigated the abilities of children with ASD in more complex social attention processes, such as joint attention or attention to distress. For instance, Dawson et al., (2004) conducted a series of tests on social orienting, joint attention, and attention to distress with 72 preschoolers between 3 and 4 years old. They found that children with ASD performed significantly worse than the control group of typically developing children, who were matched according to mental age. The study also revealed that a combination of social orienting and joint attention scores best predicted diagnosis, while joint attention alone corresponded to the best predictor of subsequent language levels in the ASD group. This further supported the evidence for the necessity of basic social attention skills in language development but also the significance of social attention in diagnosis. Altogether, studies conducted prior to the 2000s were highly informative, uncovering social attention processes affected in children with ASD. They strongly motivated the subsequent use of eye-tracking, enabling a more objective and finely tuned quantification of social attention in both neurotypical and children with ASD.

In 2002, Klin et al. used eye-tracking to explore how adolescent look at social scenes. By displaying a black and white movie "*Who's afraid of Virginia Woolf?*", they observed a reduced time spent on the eye-region within the ASD group. Interestingly, they found that the time spent on the mouth was correlated with social skills, as increased time on the mouth was associated with decreased social symptoms, suggesting a compensatory mechanism. Although this study has been widely publicized and has contributed significantly to our understanding of social attention in ASD, today's paradigms of choice when studying social orientation early during development are visual preference paradigms. These are mostly favored because of their ease of interpretation and administration. Visual preference paradigms generally consist of the simultaneous presentation of two stimuli on a split screen and the computation of the percentage of time spent on each side of the screen. A significant difference for either one or the other side of the screen is interpreted as a preference. Based on our knowledge of typical development, we assume that as long as a social stimulus is presented on one side, it should be preferred by typically developing individuals. Some studies have used even very simple stimuli to demonstrate basic social attention impairments in ASD. Klin et al., (2009) presented light points representing bodies recorded by motion capture to 2-year-old children. They displayed the light points in an upright orientation on one side and an inverted one on the other. The eye-tracking results showed that children with ASD did not exhibit any preference, while TD and even developmentally delayed (DD) children preferred to look at the light points in the upright configuration. This study significantly contributed to the promotion of visual preference paradigms by demonstrating compelling results even when using stimuli with minimal social valence.

Figure 17 - Screenshot of stimuli presented during Pierce et al's study (2011)

A prominent study in the field is that of Pierce and colleagues (2011, 2016) who designed a 1-minute visual preference task presenting social and geometric stimuli (see Fig.17). Social stimuli consisted of film clips of children doing yoga (Yoga Kids) and moving erratically, while geometric stimuli featured videos extracted from screen savers moving repetitively. Within the ASD group, they identified two subgroups of children with distinct patterns of visual exploration. The first group was labeled "geometric responders" (GR), as they focused more on geometric stimuli, and the second group as "social responders" (SR), as they predominantly looked at social stimuli. The authors found that the GR group displayed higher symptom severity scores and decreased cognitive skills compared to the SR group. Interestingly, they identified a threshold of 80% as the point at which 100% of children were diagnosed with ASD. Not only did this study reinforce the idea of decreased social attention in ASD by using an interesting and easily replicable design but also positioned social orientation as a potential early marker of ASD. Indeed, even though this decrease in orientation was not observed in all children, it was closely associated with the symptoms exhibited by the children.

Studies have shown that social attention appears to diverge ultra-early in children later diagnosed with ASD. One prospective study by W. Jones & Klin, (2013) has significantly contributed to our understanding of the early impairment of social attention in ASD. In their longitudinal study, the authors used eye-tracking to display videos of a woman talking in front of objects to high- and low-risk children (between 2 and 24 months). The results revealed that attention to the eyes decreased drastically between 2 and 6 months of age in children who were later diagnosed at 36 months of age, whereas low-risk children maintained a relatively stable attention time over the course of the study. This study has notably revealed that the social attention deficit described in individuals with ASD might not be innate but rather developmental, even if it is observed very early on. This study has also reinforced the potential use of social attention measures as early markers of ASD once again.

A task in our lab is largely inspired by Pierce's task and also presents social stimuli, videos of children dancing/moving, in contrast to geometric stimuli, which are derived from repetitively moving screensavers. This task addresses some of the shortcomings of the original task, namely, it uses fraternal twins, one boy and one girl, and counterbalances the presentation side of social and non-social stimuli. In contrast, the original task used very different children and did not counterbalance the stimuli at all. Studies conducted on this eye-tracking task yielded the same GR and SR groups as in Pierce's study. The results indicated diverging developmental trajectories depending on the children's classification. Indeed, children in the SR group showed a greater decrease in social symptom severity compared to children in the GR group one year after the intervention began (Franchini et al. 2016, 2018). These results once again confirmed a decrease in social orientation in a portion of the children with ASD and reinforced the idea that social orientation is a crucial component for children's development. Moreover, the results suggest that, in addition to being a potential marker of pathogenesis, social orientation may also serve as a predictor of outcome in young children with ASD.

Although numerous studies have emphasized social attention alterations in children with ASD, it is crucial to acknowledge that not all studies have yielded consistent results. The choice of stimuli appears to be a significant factor in revealing social attention difficulties, with static stimuli proving less sensitive than dynamic stimuli involving complex social interactions (Chevallier, Parish-Morris, et al., 2015). Additionally, compensatory mechanisms seem to emerge during the development of individuals with ASD, resulting in a notable age effect. Tasks more readily reveal atypical visual exploration of social scenes in childhood as opposed to adolescence or adulthood. Even tasks sensitive during childhood may quickly become less effective with slightly older children. For instance, Pierce et al.'s (2011) paradigm has been suggested to be less sensitive from the age of 4 onwards.

In conclusion, social attention in autism is a critical area of research that has significantly improved our understanding of the social difficulties experienced by individuals with ASD. Eye-tracking studies have substantially contributed to this understanding, emphasizing atypical social attention from an early age and constituting a relatively extensive body of literature in autism research. Despite rapid advancements in this field, several questions remain unanswered, and further investigation is needed. Urgent areas to explore include understanding the reasons behind the wide variations in social attention among individuals with autism, identifying the specific consequences of reduced social orientation during early stages, throughout their developmental paths, and on the efficacy of various interventions. In recent years, studies have started focusing on visual exploration parameters as moderators or predictors of development, considering their significant role in children's development (Carette et al., 2020; Vivanti et al., 2013, 2014). Investigating these aspects can lead to multiple benefits, such as the development of early diagnostic tools and targeted interventions, which can improve the quality of life and long-term outcomes for individuals with ASD. Furthermore, a deeper understanding of social attention in autism can inform educational strategies, facilitate social integration, and contribute to a more comprehensive understanding of the diverse experiences of individuals with ASD. By addressing these pressing questions and exploring the complexities of social attention in autism, researchers can continue to make strides toward enhancing the lives of individuals with ASD and their families, ultimately fostering a more inclusive and supportive society.

# Third section summary

In this section, we have addressed the complex nature of social attention, which encompasses various aspects of social behavior such as attention, behavior, and motivation. Social attention plays a crucial role in a child's development, as humans predominantly learn from others. It is essential for the development of imitation, which enables us to progressively gain autonomy, and language, a key feature of human communication. The autism literature highlights deficits in social attention across these different aspects. From a neurobiological standpoint, numerous brain characteristics of individuals with ASD suggest atypical processing of social information. Behaviorally, challenges in social interaction and eye contact, considered core symptoms of the disorder, further indicate a deviation in social attention compared to neurotypical development. Over the years, eye-tracking studies have amassed substantial evidence of atypical social orientation and an overall unusual visual exploration of social scenes in individuals with ASD from a very early age. However, the extent, diversity and causality of this atypical social attention remain poorly understood, necessitating further research. In summary, understanding social attention in autism is critical for comprehending the diverse experiences of individuals with ASD and addressing their unique needs. Continued research in this area will contribute to a more comprehensive understanding of autism and inform targeted interventions, ultimately enhancing the lives of individuals with ASD and their families.

## 1.4 Filling the gap: aims of the project

The current thesis project was set within the Geneva Autism Cohort (Franchini et al., 2016) , supervised by the Pr. Schaer, which is one of the largest ASD cohort in Europe. Initially started in 2012, the project aimed to follow up on children receiving early and intensive ESDM intervention to provide evidence of its effectiveness outside the US, where it was first developed. Over time, the project evolved, incorporating the follow-up of siblings of children with ASD, given their increased risk of developing ASD symptoms. Simultaneously, the project expanded to include the follow-up of older children to investigate the relationship between ASD and attentional deficits, considering the high comorbidity of ADHD within the ASD. The cohort's current objective is to longitudinally observe and understand the development of autistic symptomatology in children with various interventions, backgrounds, and comorbidities. Behavioral, eye-tracking, EEG, and fMRI assessments are part of the protocol to ensure comprehensive phenotyping. The participants' ages currently range from 3 months for the youngest to 12 years for the oldest.

Drawing from the rich and expanding data of this cohort, my project concentrated on two interconnected areas. My first research direction focused on heterogeneity in ASD. Throughout my studies, I have investigated the heterogeneity in children with ASD and the variability in their responses to various interventions. I was particularly interested in the role that basic social attention skills could play in shaping children's profiles in terms of abilities and intervention response. As demonstrated in this introduction, heterogeneity in autism remains a field where additional research is necessary, given the widely divergent responses to interventions observed across different studies. Investigating this topic was crucial for better understanding ASD etiology and providing more targeted interventions to enhance the quality of life for children and their families.

My second research area delved deeper into social attention using eye-tracking. As previously discussed, more research is needed to fully grasp the impact of atypical exploration in children with ASD on their development. Additionally, considering the potential of gaze-contingency paradigms as therapeutic tools, I was eager to contribute to this emerging field, which currently consists of only a single study. Consequently, I combined my expertise in autism and eye-tracking to develop a pilot study using gaze-contingency in eye-tracking to boost social attention in young children with autism. This approach could potentially provide them with better foundational skills for subsequent behavioral interventions, as hinted by Chevallier et al. "*In the social motivation framework, impaired social cognition is seen as the consequence, rather than the cause, of impaired social attention. This predicts that boosting social attention in various ways (e.g., by providing explicit instructions to attend the social stimulus, increasing the relevance of the social stimulus to solve the task, or increasing the participant's intrinsic interest for the stimulus) should lead to enhanced social cognitive performance*".

# 2 – Results

Following Lemanic Neurosciences Doctoral School guidelines, this section only include summary of the results and my personal contribution for each study conducted during my thesis. For more detailed information regarding results please refer to the Annex section (6) where all articles are provided in their published version or in their current state if they were in preparation by the time of writing this work.

This result section covers the results from the following papers referred below:

*Study 1* (see Annex 6.1)*:* Robain, François & Franchini, Martina & Kojovic, Nada & Wilde, Hilary & Schaer, Marie. (2020). **Predictors of Treatment Outcome in Preschoolers with Autism Spectrum Disorder: An Observational Study in the Greater Geneva Area, Switzerland.** Journal of Autism and Developmental Disorders. 50. 10.1007/s10803-020-04430-6.

*Study 2* (see Annex 6.2)*:* Robain, François* & Godel, Michel* & Kojovic, Nada & Franchini, Martina & Wilde, Hilary & Schaer, Marie. (2022). **Distinct Patterns of Cognitive Outcome in Young Children With Autism Spectrum Disorder Receiving the Early Start Denver Model.** Frontiers in Psychiatry. 13. 835580. 10.3389/fpsyt.2022.835580.

*Study 3* (see Annex 6.3)*:* Robain, F. & Kojovic, Nada & Solazzo, S. & Glaser, B. & Franchini, Martina & Schaer, Marie. (2021). **The impact of social complexity on the visual exploration of others' actions in preschoolers with autism spectrum disorder**. BMC Psychology. 9. 10.1186/s40359-021-00553-2.

*Study 4* (see Annex 6.4)*:* Robain F, Godel M, Kojovic N, Franchini M, Journal F, Schaer M. (2022) **Measuring social orienting in preschoolers with autism spectrum disorder using cartoons stimuli.** J Psychiatr Res. Dec;156:398-405. doi: 10.1016/j.jpsychires.2022.10.039. Epub 2022 Oct 21. PMID: 36323142.

*Study 5* (see Annex 6.5)*:* Robain F, Godel M., Franchini M., Schaer M. (*in prep.*) **Measuring the impact of face levels of realism on visual exploration of children with Autism Spectrum Disorder.**

*Study 6* (see Annex 6.6)*:* **Social orienting remediation using eye-tracking in preschoolers with Autism Spectrum Disorder: a randomized controlled trial.** Swiss National Clinical Trials, ID du protocole: 2022-00413.

## 2.1 Study 1: Predictors of Treatment Outcome in Preschoolers with Autism Spectrum Disorder: An Observational Study in the Greater Geneva Area, Switzerland

Robain, François & Franchini, Martina & Kojovic, Nada & Wilde, Hilary & Schaer, Marie. (2020)

*Personal contribution:* I collected data, conducted statistical analyses, and wrote the manuscript with the help of all co-authors. As it was my first scientific publication, I was particularly mentored by Martina Franchini regarding potential statistical analyses as well as discussion ideas.

*Summary*: In view of the substantial heterogeneity in response to intervention in ASD, we explored potential predictors of outcomes in two groups of children with ASD. The first group (n=22) received a uniform, intensive ESDM-based intervention, while the second group (n=38) underwent treatment available within the community (CT; e.g., speech therapy). We examined whether the type of intervention, child's age at baseline, intensity of the intervention, level of social orienting, and cognitive skills at baseline predicted changes in autistic symptoms and cognitive development after one year of intervention.
For our analyses, we performed repeated measure ANCOVA to identify changes over time, stepwise regression to pinpoint predictors of outcome, and pairwise comparisons to highlight within and between group differences. Results revealed that age at the start of the intervention, particularly access to early and intensive intervention (ESDM), was the best predictor of treatment outcome, aligning with the most recurrent predictor in the literature. Intensity of intervention or levels of social orienting alone did not predict response to intervention, meaning that more hours of weekly intervention or increased social orientation were not associated with greater outcomes after one year. Cognitive skills at baseline predicted changes in cognitive skills over time. Contrary to the common belief that children with greater cognitive skills respond better to interventions, our results showed the opposite: children with lower scores made more cognitive improvement.

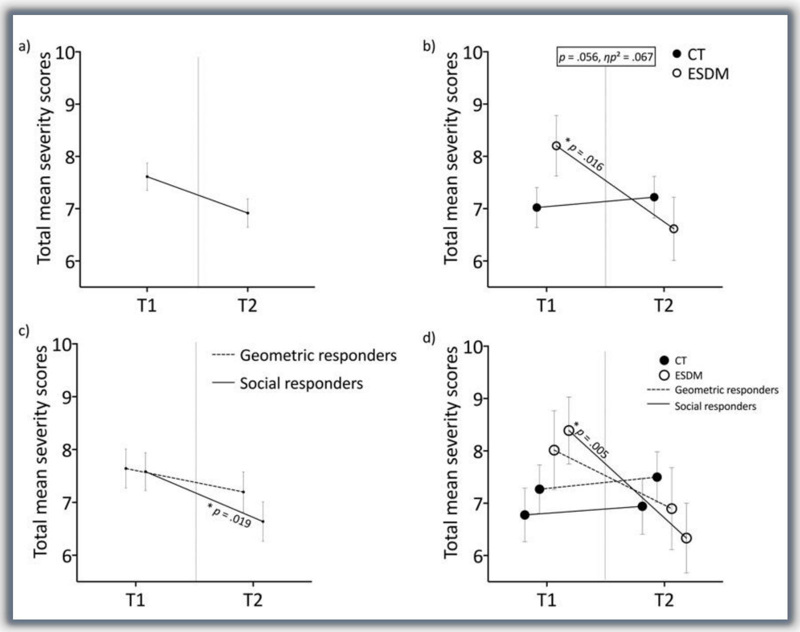


Figure 18 – Total symptom severity changes over time **a)** Total overall mean severity scores at baseline and after 1 year of intervention **b)** Total mean severity scores at baseline and after 1 year of intervention by Intervention group (ESDM vs. CT) **c)** Total mean severity scores at baseline and after 1 year of intervention by Social orienting group (Social responders vs. Geometric responders) **d)** Total mean severity scores at baseline and after 1 year of intervention in ESDMxGeo, ESDMxSoc, CTxGeo and CTxSoc.

Following these findings, we conducted post-hoc analyses, which showed that children with low levels of cognitive skills at baseline who significantly decreased their maladaptive behaviors during the first year of intervention experienced the most cognitive improvements during this period. We then divided our intervention groups into two subgroups based on their levels of social orienting, with one group of children who looked at social stimuli more than 50% of the time (Social Responders, Soc) and another group who looked at geometric stimuli more than 50% of the time (Geometric Responders, Geo) during our visual preference eye-tracking task at baseline (see Annex 6.7 – Study 1 for video examples). This distinction allowed us to observe that within our intervention groups (CT vs ESDM), children who made significant progress in the ESDM group during the first year belonged to the Soc subgroup, while children from the Geo subgroup progressed at a slower pace (see Fig.18 d). Within the CT group, children from the Geo subgroup tended to increase their RRB symptoms over time, whereas children in the Soc subgroup demonstrated stable levels of symptoms, suggesting that baseline levels of social orienting might protect against an increase in symptom severity over time. These results refine the understanding of social orienting as a predictor of intervention outcome and position it as a potential moderator of intervention.

In summary, our study demonstrated that children who entered an intensive and homogeneous intervention (such as ESDM) at a young age and exhibited some degree of preference for social stimuli were likely to make rapid progress during their first year of intervention. Moreover, we found that cognitive skills can be improved, especially when there is room for improvement and if the child decreases their maladaptive behaviors.

## 2.2 Study 2: Distinct Patterns of Cognitive Outcome in Young Children With Autism Spectrum Disorder Receiving the Early Start Denver Model

Robain, François* & Godel, Michel* & Kojovic, Nada & Franchini, Martina & Wilde, Hilary & Schaer, Marie. (2022)

*Personal contribution*: I co-authored the manuscript of this study with Michel Godel. Here, I have mostly taken part in the writing process, advised some analyses while my colleague conducted most of the statistics. I also took part in the data collection as these data are part of the longitudinal cohort started and supervised by Marie Schaer.

*Summary*: In this study, we sought to decipher the developmental trajectories of 55 preschoolers with ASD (mean age around 28 months) who underwent a full two years of early and intensive intervention based on the ESDM model. We previously investigated predictors of outcome over a year of treatment and identified variables moderating the effects of the ESDM intervention. Using cluster analyses, we aimed to identify potential profiles of response to this homogeneous intensive intervention and, by extension, personal characteristics that could potentially predict greater responsiveness. Our results revealed three distinct patterns of response over time within our sample (see Fig.19). The first group of children High at Baseline (HB) had minimal cognitive delay and improved their

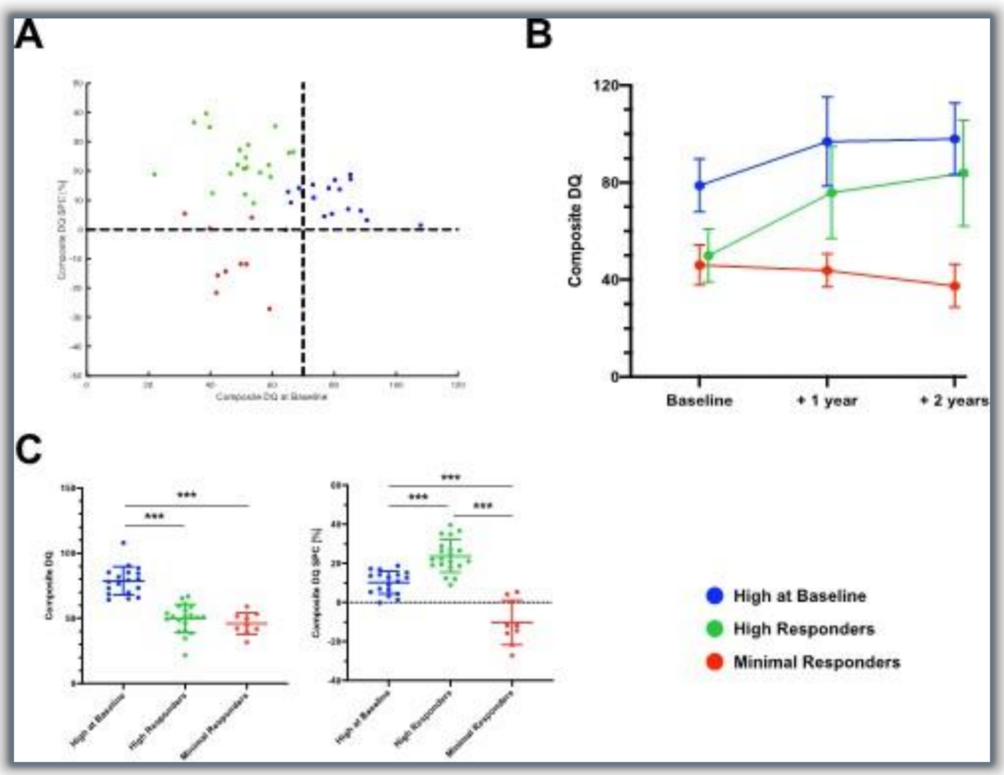


Figure 79 – **a)** Individual values of the two measures used in the clustering analysis algorithm (composite DQ at baseline and DQ SPC over the 2 years of interventions). Color code represents the cluster membership of each participant after the application of the cluster analysis. **b)** Composite DQ trajectories of the three subgroups parsed by the cluster analysis. **c)** Differences between the three subgroups on the two measures that were used to parse them. ****p < 0.001. DQ, Developmental quotient; HC, Higher cognitive; MinR, Minimal responders; OptR, Optimal responders; SPC, Symmetrized percent change.*

cognitive skills over the two years of intervention. The other two groups presented with significant cognitive delay at baseline but different patterns of response over time. The first group High Responders (HR) significantly improved their developmental scores, while the other group Minimal Responders (MR) exhibited more subtle progress over time. Our analyses did not identify any characteristics that differentiated between these groups with lower developmental skills at baseline. However, we found an association between better adaptive functioning skills at baseline and rapid developmental skill changes within the first six months of intervention, which was typical of the HR group. In other words, children with more severe profiles at the beginning of the intervention who demonstrated rapid progress at the outset were most likely to have made progress by the end of the two-year intervention, whereas children who did not progress at the beginning remained stable.

Overall, our results underscored once again the great heterogeneity of response within ASD. Children with high skills at the beginning of the intervention all seemed to progress, while children with low skills appeared more challenging to discriminate. Rapid progress by six months of intervention seemed to be the most effective indicator of overall progress by the end of the intervention. These findings could influence how we assess progress and contribute to a rapid re-evaluation of the needs of children making slower progress during an intervention program.

## 2.3 Study 3: The impact of social complexity on the visual exploration of others' actions in preschoolers with autism spectrum disorder

Robain, F. & Kojovic, Nada & Solazzo, S. & Glaser, B. & Franchini, Martina & Schaer, Marie. (2021)

*Personal contribution*: For this study, I actively participated in data collection, conducted statistical analyses, and wrote the manuscript. I received input from my co-authors to improve the manuscript. The eye-tracking task was already designed, and data partially collected when I arrived in the lab. It was conceived by Martina Franchini and Marie Schaer.

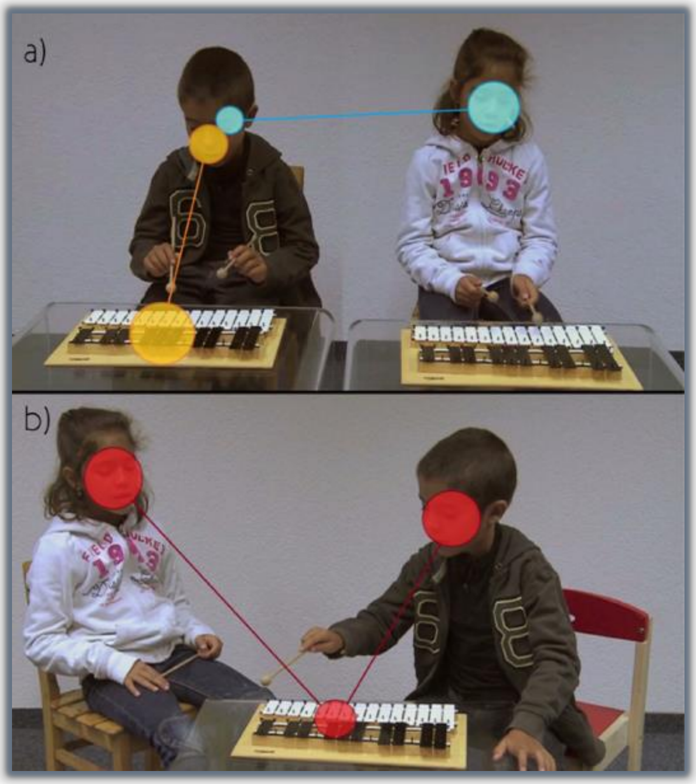


**Figure 20** – Sample of eye-tracking tasks **a)** Parallel play condition. Blue dots and line represent Face to Face gaze shift. Yellow dots and line represent Face to Object gaze shift. **b)** Interactive play condition. Red dots and lines represent Face-Object-Face triangle gaze shift.

*Summary*: Given the importance of social attention in early development and the rapidly changing complexity of social scenes, we investigated how children explore social interactions and to what extent social complexity influences their visual exploration. To do this, we used an eye-tracking task featuring twin children playing either in a parallel (see Fig.20 a) or interactive way (see Fig.20 b; see Annex 6.7 – Study 3 for video replay). We compared the gaze patterns of typically developing (TD) children (n=26) to those of children with ASD (n=37), with an average age of 3.5 years. We employed repeated measures linear models to analyze the time spent on faces, objects, and body parts, as well as fixation duration on these areas of interest (AOI). Additionally, we investigated the relationship between visual exploration patterns and behavioral measures (e.g., symptom severity, adaptive and cognitive skills).
Our findings revealed a general decrease in time spent on faces in the ASD group compared to the TD group, suggesting an overall reduced social attention in ASD (see Fig.21). Moreover, our results showed that children increased their time spent on objects and decreased time on bodies when transitioning from

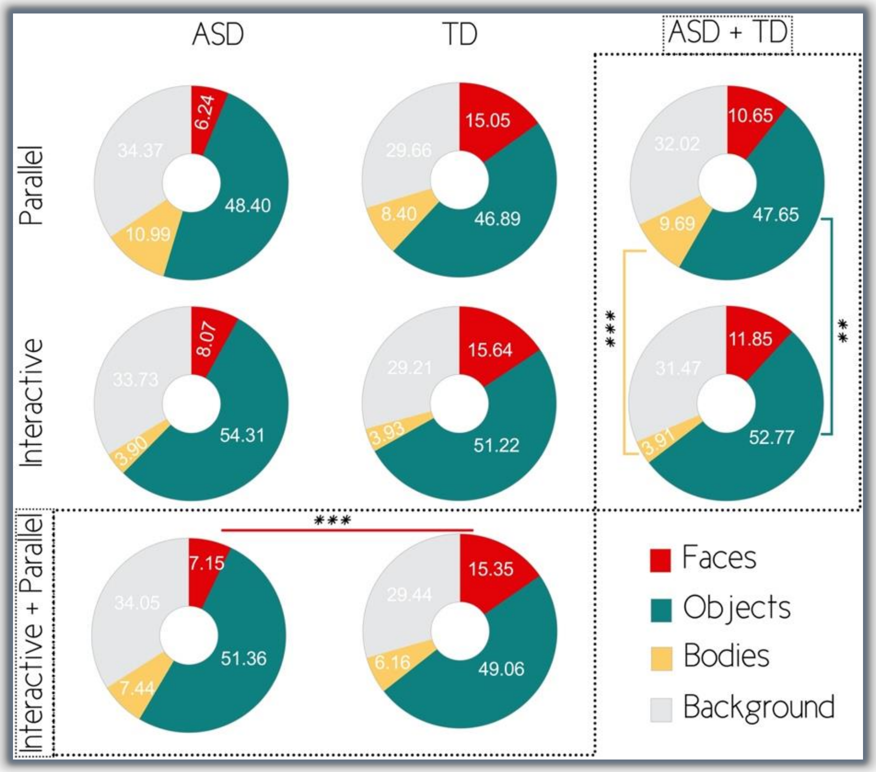


**Figure 21** - Percentage of time spent per AOI as a function of condition (in lines) and group (in columns). Brackets represent significant differences **p < .05; **p < .01; ***p < .001*

parallel play scenes to interactive social scenes. Fixation duration also tended to decrease when watching interactive scenes compared to parallel ones, indicating shorter gazes, and increased visual exploration dynamism. Gaze shifting between objects and faces also increased in the interactive condition, further supporting greater dynamism compared to the parallel condition. These gaze pattern alterations induced by the social complexity/interaction of the scene were observed in both groups, though to a lesser extent in the ASD group.

Regarding correlations between behavioral measures and gaze patterns, we observed that lower adaptive skills were correlated with decreased time spent on faces and increased time spent on bodies. Our results also showed that increased symptom severity was associated with increased fixation duration on several AOIs.

Overall, our findings suggest that social complexity has a clear impact on visual exploration patterns in both TD and children with ASD. Our results reinforce the notion of an inherent decreased attention to faces and social stimuli overall in ASD. Lastly, our results indicate that children who were less affected by the increase of social complexity, and who did not dynamize their visual exploration, were the ones who were more affected, exhibiting more symptoms or lower adaptive skills, for example.

## 2.4 Study 4: Measuring social orienting in preschoolers with autism spectrum disorder using cartoons stimuli

Robain F, Godel M, Kojovic N, Franchini M, Journal F, Schaer M. (2022)

*Personal contribution*: I imagined stimuli with the help of Marie Schaer as well as inputs from my younger brother David Robain, who drew the stimuli and animated them. I designed the task, participated in data collection, analyzed data, and wrote the manuscript with the help of my co-authors.

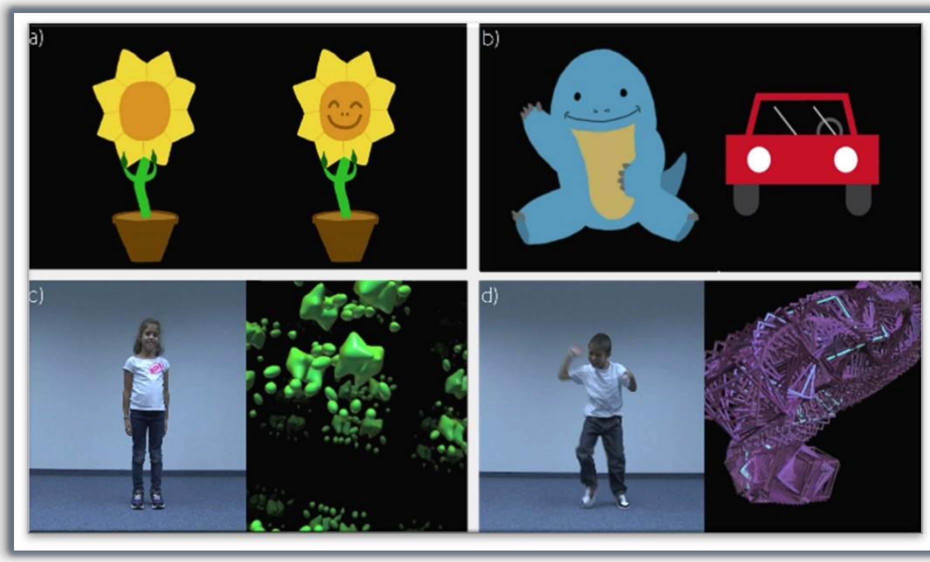

Figure 22 – Sample the Cartoon and Realistic tasks **a)** Screenshot from the Cartoon task: flowers moving and dancing **b)** Screenshot from the Cartoon task: monster waving and car whipping its windshield **c)** Screenshot from the Realistic task: young girl and geometric shapes moving **d)** Screenshot from the Realistic task: young boy and geometric shapes moving.

*Summary*: In this study, we aimed to investigate whether the observation of very simple social stimuli in the form of cartoons would elicit the atypical visual social attention observed when viewing realistic stimuli. To do so, we used two visual preference tasks. The first task (Realistic task, see Fig.22 c & d) employed videos of children as social stimuli, versus repetitively moving geometric shapes as non-social stimuli. The second task (Cartoon task; see Fig.22 a & b) used minimally social stimuli, such as cartoon stimuli, opposed to movement-matched non-social stimuli (see Annex 6.7 – Study 4 for video examples). We compared the visual preferences of 90 children with ASD to 20 TD children, aged approximately 3 years old.

We used ANCOVAs to compare the percentage of time spent on areas of interest (AOIs), social or non-social, in both tasks, as well as more refined gaze parameters such as fixation duration, first fixation, and orientation speed, for example. We also investigated correlations between visual exploration patterns and behavioral measures such as symptom severity, cognitive skills, and adaptive behavior levels.

Our results revealed that both TD and children with ASD preferred to look at social stimuli during the Cartoon task, but this was not the case during the Realistic task (see Fig.23). Indeed, on average, children with ASD did not show any preference between social and non-social stimuli during the Realistic tasks, leading to decreased social orientation compared to TD children. As previously described in similar studies, social orienting was extremely heterogeneous in the ASD group.

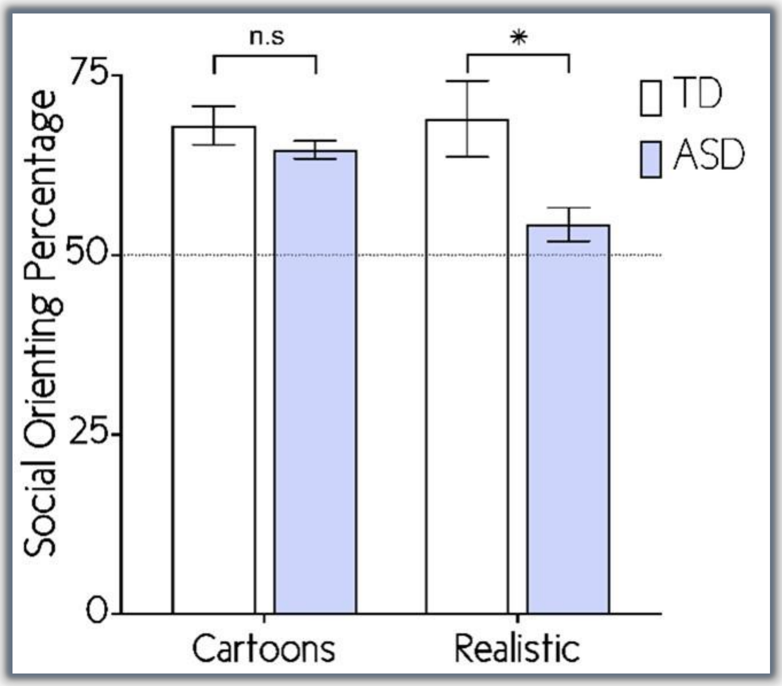


**Figure 23** – Mean percentage of time spent looking at the social part of the screen in the Cartoon and Realistic task of both groups. *$^*p < .05$*

Despite the absence of atypical social attention within the Cartoon task, we identified numerous correlations between behavioral measures and visual exploration patterns when watching the Cartoon task. Indeed, during the Cartoon task condition, we observed significant correlations between decreased social orienting percentage, increased fixation duration, decreased number of fixations, decreased social prioritization, and increased cognitive delay as well as decreased adaptive skill levels. These results suggest that although there was no difference in average preference between the groups, an exploration deviating from the norm could be indicative of a developmental delay. Since these correlations were not observed in the Realistic task, it is possible that the Cartoon task is less effective in distinguishing diagnosis but more sensitive to developmental delay through the analysis of finer visual exploration parameters.

Overall, our results pointed towards no difference in preference when watching minimally social stimuli versus non-geometric movement-matched stimuli in ASD. However, significant associations were found between developmental and adaptive levels with more refined visual exploration pattern parameters, and consistent results of atypical social orienting when watching realistic stimuli.

## 2.5 Study 5: Measuring the impact of face levels of realism on visual exploration of children with Autism Spectrum Disorder

Robain F, Godel M., Franchini M., Schaer M. (*in prep.*)

*Personal contribution*: I imagined this task following discussions during my mid-term exam. I designed the task, created all stimuli, participated in data collection and am currently analyzing data as well as writing the manuscript.


**Figure 24** – Sample stimuli from all conditions **a)** Realistic face **b)** Avatar face **c)** Cartoon face


*Summary*: Considering the preference for social over non-social cartoons in our precedent study, we aimed to investigate if having a simpler face was enough to smoothen the atypical social attention within ASD. The aim of this task was therefore to investigate how face stimuli were explored according to their levels of realism. For this purpose, we designed a gaze-contingent task where children had to look at faces that were: cartoons, avatars, or realistic (see Fig.24). A mask of 5° of visual angle was applied on the faces to make sure no areas were processed in the peripheric visual field (see Annex 6.7 – Study 5 for video examples). We explored the time spent on different the upper/lower parts of the face, eye/mouth areas of interest (AOIs) within a group of 30 children with ASD and a group of 11 TD children of approximately 5 years old. We conducted repeated measures general linear model to investigate the effect of condition in our sample. We also investigated within and between group differences. Finally, we performed correlation to investigate the association between visual exploration patterns and behavioral measures. Our results showed that children looked more or less the same across conditions, meaning that they spent the same percentage of time looking at the different AOIs (see Fig.25 b). This led to a similar effect of condition within both groups (see Fig.25 c). Indeed, children from both groups looked more at the eye region during the Cartoon and Realistic conditions compared to the Avatar condition. During the latter, children all looked significantly more to the lower part/mouth region, compared to the two remaining conditions (see Fig.25 a). In addition, our results highlighted an overall increased number of fixations across all conditions within the ASD group compared to the TD.

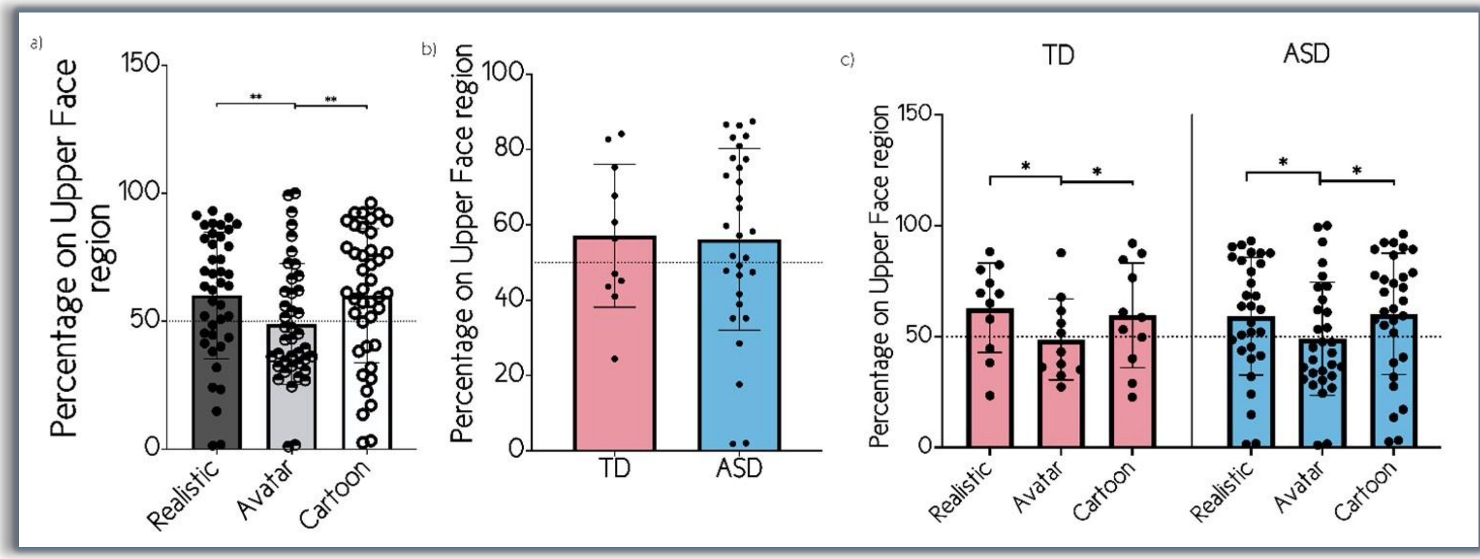


Figure 25 – Percentage of time spent on Upper Face region **a)** Percentage on the Upper Face region by condition **b)** Percentage on the Upper Face region by group **c)** Percentage on the Upper Face region by group*condition

Investigating the percentage of time spent on screen, we also observed that the Cartoon condition appeared as the most interesting for our children in our sample as the percentage was significantly higher. Finally, correlations analyses highlighted several significant associations. Older kids tend to do more numerous fixations, look less at the eyes in the Realistic and Cartoon conditions. Higher developmental and adaptive skills were associated with increased time spent on the lower part of faces in the Realistic condition.

Overall, our results did not support the reduced attention to the eyes typically described in individuals with ASD. The hypothesis of more intensive exploration in relation to the mask is suggested but not highly likely. The main result is that TD and children ASD seem to have patterns of exploration that are identical as a function of the level of realism, indicating that it would be relevant to use cartoon stimuli for remediation in virtual reality, for example, since TD and ASD explore them in the same way. On the other hand, our results suggest a form of avoidance during the Avatar condition, which is possibly linked to an uncanny valley effect. It would therefore be useful to understand to what extent an avatar becomes unpleasant, as their use could lead to inconsistent results across studies.

## 2.6 Study 6: Social orienting remediation using eye-tracking in preschoolers with Autism Spectrum Disorder: a randomized controlled trial

Robain F., Godel M., Solazzo S., Latrèche K., Franchini M., Schaer M. (*ongoing*)

*Personal contribution*: I imagined and designed this randomized controlled trial with the help of my supervisor Marie Schaer. I designed and created all stimuli used in this remediation protocol. I also wrote and submitted the ethic committee to get required approval for this project to begin. I coded all tasks of the study using Matlab and Tobii SDK. Finally, I carried out the eye-tracking sessions with the children and processed preliminary data.

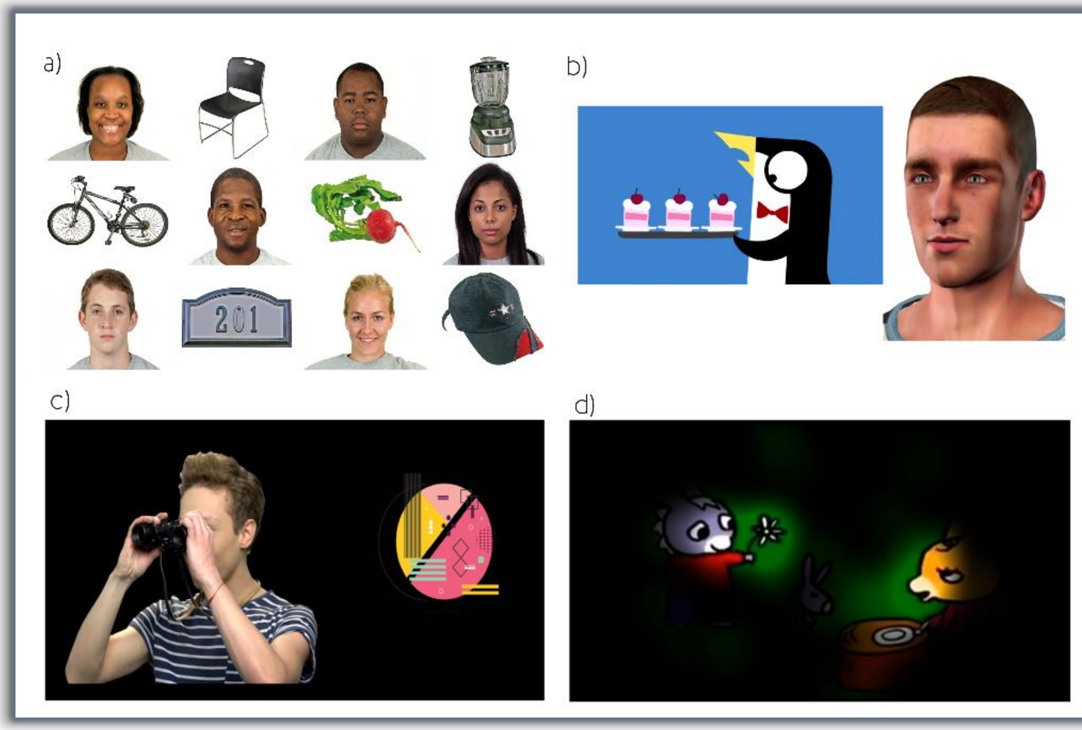


Figure 26 - Sample of the 4 tasks proposed during a remediation session **a)** Task 1 : Screenshot of an array including 3 happy faces, 3 neutral faces, 3 men, 3 women, 3 high interest objects, 3 low interest objects **b)** Task 2: Screenshot of the penguin cartoon and the avatar watching the cartoon **c)** Task 3: Screenshot of an activated social stimulus opposed to a non-moving geometric shape **d)** Task 4: Screenshot of masked Trotro cartoon to represent TD like visual exploration

*Summary*: Based on my previous studies that highlighted the level of social attention as a potential moderator of the intervention, I aimed to design a clinical trial to increase social attention before an intervention, and therefore enhance the response to it. During this clinical trial, we aim to enhance social orientation using gaze contingent paradigms over 6 sessions of eye-tracking. We use a randomized controlled trial (RCT) design to get two groups, one receiving the remediation (REM) and one receiving a sham version of the remediation tasks (SHAM). Sham tasks were non-contingent, and the stimuli were activated randomly. The clinical trial is ongoing by the time of writing these lines, but groups should end up including 20 participants aged between 1.5 to 5 years old. The task 1 consists in an array of images including faces and objects. Children looking at faces activate some joyful music playing in the background (see Fig.26 a; see Annex 6.7 – Study 6 – Task 1). Task 2 consists of a cartoon playing with an avatar watching on the side. There are several pauses during the cartoon and watching at the avatar instantly resumes the cartoon (see Fig.26 b; see Annex 6.7 – Study 6 – Task 2). Task 3 consists of people doing random actions side by side with abstract geometrical stimulus. Looking at the social stimulus activates music and colors (see Fig.26 c; see Annex 6.7 – Study 6 – Task 3). Task 4 consists of a Trotro cartoon playing. Looking at the cartoon in an atypical way (based on visual exploration of TD children), activates a mask that hides everything not typically observed (see Fig.26 d; see Annex 6.7 – Study 6 – Task 4). As primary outcome measures, we investigate changes in visual exploration of 3 non-contingent eye-tracking tasks that measure social orienting as well as 3 parental questionnaires. We also investigate changes in several variables during and across all remediation sessions. We use repeated measures general linear modeling to investigate those changes over time. We also conduct t-tests to explore differences between and within groups. Our results are currently extremely preliminary as only 7 children completed the trial and should be considered cautiously. The first results point to an overall decreased interest for the tasks among the SHAM group compared to the REM group. Indeed, the percentage of time spent on screen was decreased in the SHAM group compared to the REM group, suggesting that the contingency might maintain interest for the stimuli over time.

Results from the first task (see Fig.27) indicate a higher time spent looking at happy faces in the REM group compared to the SHAM group. This is led by a progressive increase in time spent on these faces (but not neutral faces) in the REM group whereas children from the SHAM group increase their time spent on objects and especially objects associated with frequently reported restricted interests in autism (HIA).

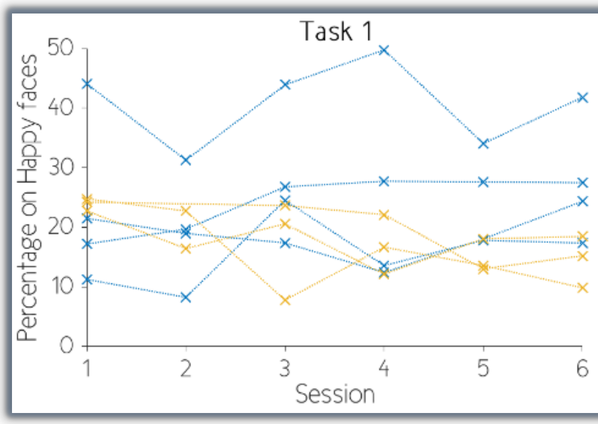


Figure 27 – Mean percentage of time spent on Happy faces during the Task 1.

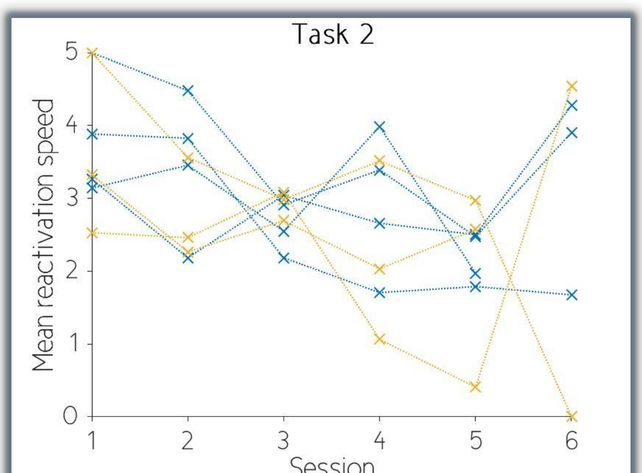


Figure 28 – Mean speed to look at the avatar face during pauses during Task 2

Results from the second task (see Fig.29) indicate that children from both groups appear to associate the avatar's face with pauses and turn more and more quickly over time towards it during breaks to resume the cartoon. It also appears that children from the SHAM group look at the avatar's face more insistently than children from the REM group.

Results from the third task (see Fig.29) highlighted significant differences in time spent on the social side of the screen between groups, in favor of the REM group. In addition, children from the SHAM group tend to decrease their percentage of time spent on the social side over time. Interestingly, different clusters of profile seem to arise from these preliminary results, one with high percentage at baseline and another one with lower percentage at baseline each one having an evolution that seems different as a function of the intervention group.

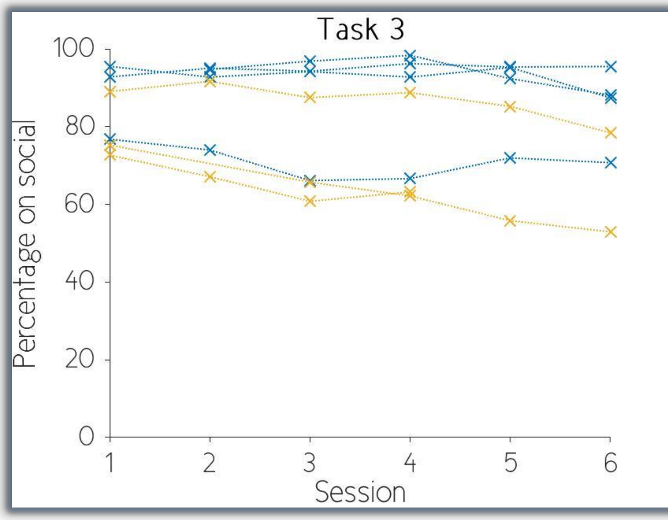


Figure 29 – Mean percentage of time spent looking at the social side of the screen during Task 3

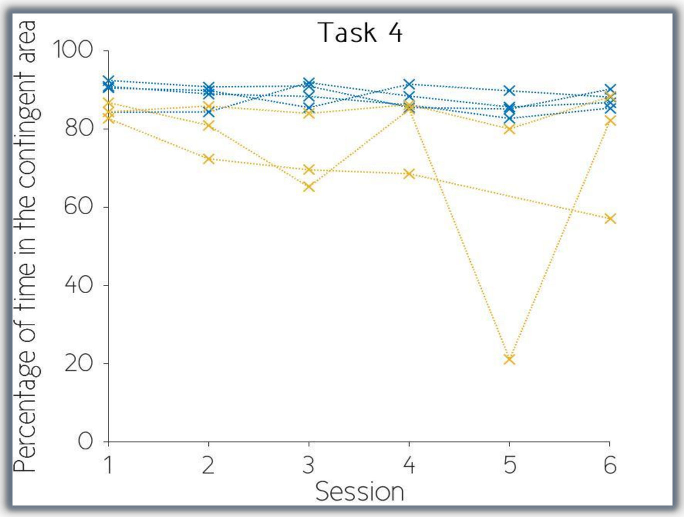


Figure 30 – Mean percentage of time spent looking at the typical AOIs during Task 4

Children from the REM group spent more time looking typically compared to children from the SHAM group during the fourth task (see Fig.30). In other words, the contingent mask effectively reoriented the attention of children from the REM group.

As of now, no significant effects were identified regarding the non-contingent eye-tracking tasks and questionnaires assessed at baseline and outcome.

# 3 – Discussion

This thesis is primarily supported by the articles outlined in the preceding section. Each of these papers already contains a discussion, at least for those that have been published. As a result, we will briefly summarize the discussions of these papers and link them to the two main axes of this thesis : the first one being the investigation of the potential predictors of outcome in Autism Spectrum Disorders (ASD) and the investigation of the heterogeneity in autism overall; the second axis being more focused on the atypical visual exploration in autism going from low levels of visual preference to the whole dynamic process when watching social interactions. We will conclude by discussing the preliminary results from the RCT and then provide a perspective on future developments arising from this thesis project.

## 3.1 Predictors of outcome and heterogeneity in autism

In the first half of my research, I focused on the pervasive heterogeneity in autism, particularly the heterogeneity of response to intervention. Considering studies that identifies early social attention levels as a potential early biomarker of ASD (W. Jones & Klin, 2013; Pierce et al., 2016), I aimed to explore whether social attention levels might additionally play a role in predicting the response to intervention.

In Study 1, we investigated potential predictors of progress in children with ASD, some of whom received an Early Start Denver Model (ESDM) intervention, while others received community-based treatments (CT). The results aligned with various studies on response to intervention, emphasizing greater progress in children receiving early and intensive intervention (Dawson, 2008; Eldevik et al., 2009; Fuentes et al., 2021; Landa, 2018; Zwaigenbaum et al., 2015). Notably, the results revealed improvements in communication among children in the ESDM group, echoing similar findings from ESDM studies (Dawson et al., 2010). Moreover, as ESDM specifically targets improving social communication during the initial stages of intervention (Rogers & Dawson, 2010), this result was consistent with the values and objectives of the intervention model. Interestingly, intervention intensity alone did not predict outcomes, suggesting that intensity must occur within the context of early intervention to capitalize on brain plasticity during critical developmental windows (Dawson, 2008; Ismail et al., 2017). This notion is supported by previous studies showing that intensive interventions show decreased effectiveness beyond a certain age (Granpeesheh et al., 2009). The fact that intensity alone did not predict outcomes indicates that providing a highly intensive intervention by itself is insufficient for efficacy and indirectly supports the "precision medicine" movement (König et al., 2017). This movement advocates for greater consideration of individual characteristics and needs to favor the development of more tailored interventions for everyone, including personalized hours of intervention. I believe it is indeed worth questioning the relevance of intervening very intensely with a child who quickly gets exhausted, for example, even within the context of early intervention. Keeping this in mind, it might be interesting to investigate the effects of an ESDM-type intervention while adapting the intervention hours to the child's needs and capacity.

In addition, we also showed during this study that children with low cognitive levels were the ones who benefited the most from the interventions, precisely by increasing their cognitive levels. This is in contrast to numerous studies that often highlight a high cognitive profile as a predictor of response to intervention (Anderson et al., 2007; Fernell et al., 2011; Harris & Handleman, 2000; Tiura et al., 2017). Our results seem more in line with those of Reed, (2016), who suggested that cognitive gains and cognitive skills at baseline had an inverted U-shaped association, with a peak in gains among children with IQs between 50 and 80. These children benefited the most from interventions, particularly because they had the most to gain. We also conducted post-hoc analyses demonstrating that among these children who made significant progress, those who reduced their maladaptive behaviors the most were the ones who showed the most improvement. These findings support the idea that lower IQs are generally associated with more maladaptive behaviors (Shattuck et al., 2007; Woodman et al., 2015), which may be partly explained by difficulties in assessing IQ. Given this, intervening on maladaptive behaviors in children with low IQ might result in IQ gains over time. Overall, our results indicate that all children, without exception, can benefit from intervention and that children with good cognitive skills should not be prioritized. Finally, this first study also highlighted patterns of progress within the groups themselves, particularly based on their level of social attention at the beginning of the intervention. We observed that children who made significant progress within the ESDM group were those with relatively high interest in social stimuli at the beginning of the intervention, while children with a preference for geometric stimuli progressed much more slowly. In the CT group, children preferring geometric stimuli worsened their repetitive symptoms, while others showed relatively stable symptoms. These findings position social attention as a moderator/potentiator of early intervention. Moreover, these results support the social motivation theory (Chevallier, Parish-Morris, et al., 2015), which posits a deficit in social attention as the beginning of a developmental cascade. Indeed, it appears that children with social attention skills closer to the norm are the ones who experience faster progress from intervention, potentially because they are more readily able to pay attention to their therapist from the beginning of the intervention, reinforcing the importance of social attention in the development of early socio-communication skills. Following this finding, we hypothesized that children who did not show significant progress during the first year might experience later progress, notably through the enhancement of social attention throughout ESDM sessions.

Interestingly, the second study conducted on response to intervention provided a direct answer to this hypothesis. In this follow-up research, we continued to explore the response to intervention but this time with a focus on the presence of distinct developmental clusters among children undergoing the same treatment, as underscored in our initial study. This study examined the different patterns of progress within the ESDM intervention over a 2-year period, which is the total duration of the intervention, and used cognitive gains as an outcome measure. Firstly, our findings revealed overall cognitive gains that enabled 72% of the children included to attend regular education classrooms, suggesting that the ESDM intervention model is equally effective (Dawson et al., 2010) in Europe as it is in the United States, despite potential cultural differences. Furthermore, our results showed that children who initially had moderate cognitive delays (average IQ >70) consistently caught up on these delays during the intervention. This finding implies that clinicians can be confident in the progress a child with a moderate delay will make when recommending an ESDM intervention. However, our results also highlighted distinct subgroups within children presenting significant cognitive delays (with an average IQ < 70), with some showing notable progress and catching up on their delay (OptR), while others exhibiting improvement in their raw scores but still experiencing significant cognitive delay throughout the intervention (MinR). A closer examination of the characteristics of MinR and OptR children revealed that OptR children constituted the majority (about 70% of our sample), reinforcing the idea that most children make significant progress when receiving an ESDM intervention. The only distinguishing characteristic at baseline was their adaptive skills although it was not possible to differentiate them using only this variable. However, we demonstrated that by associating adaptive skills at baseline and early progress, we could predict group membership. In fact, children who made rapid progress in language comprehension and adaptive communication domains, which are among the main targets of social communication addressed during the ESDM intervention (Rogers & Dawson, 2010), were the ones who made significant cognitive gains by the end of the intervention.

In our first study, we discussed the possibility of a later response to intervention in children who made little to no progress during the first year. If we consider this recent finding, it appears that this phenomenon is unlikely, and that the progress made during the first year, and even within the first 6 months, is sufficient to estimate overall progress. It also appears that there will be no sudden progress during the second year if no progress were observed during the first, making the first six months a crucial timing in intervention. In summary, the results from this second study once again highlighted the heterogeneity within autism and the complexity it generates. This study strongly supported intensive and early intervention in children, considering the overall access to regular classrooms. Additionally, it provided valuable insights regarding the existence of clusters in response to intervention and the possibility of determining membership in these clusters using indicators of ultra-early progress. Closer-interval follow-ups could provide great information about a child's need and inform about the necessity of potential intervention adjustments earlier. Future studies on intervention outcomes could benefit from systematically examining the various emerging progress patterns to better comprehend the initial characteristics of different groups. This understanding would enable the development of more tailored interventions to address individual needs. Consequently, the effectiveness of interventions for children with autism would be further optimized, ensuring they receive the necessary support and resources to achieve their full potential.

## 3.2 Social attention in autism using eye-tracking

During this work, we emphasized the significance of social attention in children's development. We also reviewed the numerous brain alterations in areas associated with social attention in ASD, the social challenges central to ASD diagnosis, and the atypical visual exploration of social stimuli in at-risk children and those with ASD, from an early age. In my previous work on predictors of outcome, we validated the importance of the basic level of social orienting as a moderator of intervention response. Consequently, in the second part of my work, I explored the scope of these social attention divergences using novel eye-tracking paradigms.

In our first eye-tracking study, we aimed to examine how children with ASD visually explore other children engaging in parallel or interactive play. The premise was that observing interactive play involves greater social complexity in comparison to parallel play and should consequently alter exploration patterns. Additionally, the ability to watch such social interactions is ubiquitous in young children's environments, such as daycares, and directly shapes our understanding of object usage and future symbolic play skills. It is therefore a design close to what can be observed daily. Our findings indicated that social attention in children with ASD was indeed compromised, particularly with reduced time spent on faces in both parallel and interactive conditions. These results were consistent with a multitude of studies that report atypical attention to faces in ASD (Chawarska et al., 2010; Chevallier et al., 2012; Frazier et al., 2017; Guillon et al., 2014; Harrop et al., 2019; Key & Stone, 2012; Klin et al., 2002; Muratori et al., 2019; Parish-Morris et al., 2013). Furthermore, we showed that children with stronger social and communication skills spent more time focusing on faces, thereby emphasizing the close connection between social attention and the proper development of early socio-communicative abilities. We identified an effect of social complexity, which similarly influenced the visual attention of both TD and children with ASD. This was particularly evident in the increased time spent on objects during the interactive condition, suggesting that the shared attention of children in the task guided the attention of the children observing the task as well. This outcome was not observed in a comparable study by Shic et al. (2011). We proposed that differences in task design contributed to these discrepancies, with Shic's task being visually richer, increasing the number of distractors which might have disrupted visual exploration considering disrupted low level perception in ASD (Mottron et al., 2006), and lacking sound on a somehow complex task (puzzle solving). In contrast, our task featured a xylophone game, which more effectively captured attention through auditory stimulation (Iordanescu et al., 2010; Ocak et al., 2018) and the simplicity of the scene (McCall & McGhee, 1977). Additionally, we discovered that social complexity had a profound impact on exploration dynamics by shortening fixation durations on socially relevant areas. Interestingly, children who did not exhibit these modifications displayed more symptoms. It is possible to draw a parallel between this lack of visual exploration dynamism and the disengagement difficulties often reported in ASD (Elsabbagh et al., 2013; Goold et al., 2022; Landry & Bryson, 2004; Sacrey et al., 2014), thereby strengthening the theory of underlying attentional deficits as the source of the core deficits observed in individuals with ASD. Finally, we investigated exploration dynamics by quantifying back-and-forth gaze transitions between faces, faces and objects, and face-object-face triangulation. Our findings highlighted consistent monitoring of faces in TD but decreased monitoring in children with ASD, even among those who looked at faces. We also observed diminished face-object gazes in ASD compared to TD, although these behaviors increased in the interactive condition, supporting decreased action monitoring in ASD. Finally, similar results were discovered for face-object-face monitoring, and only a few of these action monitoring gazes were observed within the ASD group. In summary, our results demonstrate atypical social exploration characterized by reduced time spent on faces, significantly impacting the development of joint attention skills in children with ASD. The infrequent occurrence of high-level monitoring behaviors in children with ASD emphasizes the interdependence of social exploration skills, as the development of these abilities relies on establishing foundational competencies (Carpenter et al., 1998; Franchini et al., 2017; Schietecatte et al., 2012). Indeed, this study highlighted well how the development of such skills primarily involves paying attention to faces to gradually build gaze-following skills, and ultimately developing joint attention and action monitoring by observing social interactions. In essence, these skills depend on and reinforce previous levels, demonstrating their interdependent nature.

The second eye-tracking study aimed to recreate a social preference task using very simple stimuli. The idea was to create a task that could distinguish ASD from TD children based on their visual preference levels, similar to the task inspired by Pierce et al. (2011), while addressing some issues by controlling for movement and presenting more attractive stimuli for younger children. Our results showed that our Cartoon task did not reveal visual preference differences between TD and children with ASD. However, the Realistic task continued to highlight a high heterogeneity of preference in the ASD group, with TD children, on average, preferring to look at social stimuli. Discussing these results was challenging due to the relatively divergent findings. The Cartoon task results do not support the Social Motivation theory (Chevallier, Parish-Morris, et al., 2015), given the clear overall preference for social stimuli in this task among children with ASD as well. In contrast, the decreased preference for social stimuli observed in the Realistic task, positively correlated with the presence of more symptoms, aligns with the Social Motivation theory. We focused much of our discussion on the differences between these two tasks, particularly how the Realistic task poorly represents a social orienting task but rather a preference task for geometric shapes (initial goal of Pierce's task), effectively distinguishing TD from children with ASD. Indeed, the task includes numerous confounding factors such as repetitive movements for non-social stimuli, generally preferred over random movement (Wang et al., 2018), and geometric non-social stimuli, often reported as part of restricted interests in children with ASD (Klin et al., 2007; Kwon et al., 2019; Unruh et al., 2016) and associated with high perceived rewards even when presented alone (Gale et al., 2019). Conversely, our Cartoon task was designed to fully control for these different factors, largely explaining the difference in results. We also suggested the possibility that the cartoonish aspect may have induced different exploration patterns, perhaps closer to the norm by compensating the social aspect. However, there is limited information on the visual processing of cartoon stimuli in the literature, and the results are divergent (Atherton & Cross, 2021; Riby & Hancock, 2009; Rosset et al., 2008, 2010). Additionally, we identified significant correlations between visual exploration patterns and developmental and adaptive measures in the Cartoon task for participants with ASD, but not in the Realistic task. Key findings include a positive correlation between greater social orienting and developmental skills in the ASD sample, suggesting low social orienting levels in the Cartoon task may serve as an early warning for developmental delays, particularly in high-risk infants. We also observed longer fixation durations, indicative of "sticky attention" (Sacrey et al., 2013, 2014), associated with greater developmental and adaptive delays, supporting their consideration as additional red flags of early atypical development (Landry & Bryson, 2004; Sacrey et al., 2014; Zwaigenbaum et al., 2005). Furthermore, decreased social prioritization in children with ASD was linked to increased developmental delays, here bringing indirect support to the Social Motivation theory as it strengthens the link between decreased social motivation and decreased developmental skills. Together, our results emphasize the importance of examining refined visual parameters and their relationships with behavioral measures even in preference paradigms. Overall, the Realistic task was effective in differentiating TD children from children with ASD due to its ability to capture the strong interest of children with ASD in repetitively moving geometric shapes. Yet, it may not be the best task for specifically measuring social attention. On the other hand, our Cartoon task seemed to offer more control in this respect, although it did not reveal a social attention deficit in our study considering the preference percentages. One proposed hypothesis is that the children assessed in this task were already “too old”, similar to Pierce’s task, which becomes less discerning after the age of four. Preliminary, unpublished results indicated that high-risk children do not display a preference for social stimuli in this task, while low-risk children do. These findings suggest that the lack of social attention deficit observed in our main results might not be due to the use of cartoon stimuli, but rather that the task itself was not challenging enough to elicit atypical exploration patterns in the children with ASD.

Nevertheless, the results from the Cartoon study raised many questions, and it was difficult to know if the exploration of cartoon stimuli should be considered to be equivalent to realistic social stimuli. To further our understanding of our previous results and to address this gap in the literature we designed a task to evaluate the visual exploration of faces with very different levels of realism (Realistic vs Avatar vs Cartoon). We used gaze-contingency to mask the peripheral field of view, ensuring that facial features were not processed in the periphery, thereby encouraging more active exploration. Our results did not evidence differences between groups as children with ASD and TD exhibited similar proportions of visual exploration of the different areas of interest under all conditions. Our results did not align with the frequently observed decrease in attention to the eyes in the literature (Frazier et al., 2017; W. Jones & Klin, 2013; Klin et al., 2002; Pelphrey et al., 2002). This discrepancy might be due to the simplicity of the task or the presence of face masks encouraging active exploration. However, this seems unlikely given similar studies that reported reduced attention to the eye region in both clear and masked conditions (Wang et al., 2019). Interestingly, the Avatar condition led to unique exploration patterns compared to the Realistic and Cartoon conditions, possibly related to the uncanny valley effect (Feng et al., 2018). Furthermore, children with ASD who focused more on the mouth in the Realistic and Cartoon conditions exhibited better communication scores, aligning with the findings of Klin et al. (2002). This outcome suggests a potential compensatory mechanism developing with age, which encourages children with communication difficulties to concentrate visually on the source of language as a form of compensation. Additionally, our results revealed differences in time-dependent exploration between groups, with children with ASD losing interest more rapidly than TD children. This unusual visual exploration dynamic could be indicative of atypical social motivation, as proposed by the social motivation theory (Chevallier et al., 2012). Despite a limited sample size, our findings indicate that both TD and children with ASD view cartoonish and realistic faces, similarly, supporting the use of cartoonish characters for social skills remediation in children with ASD. However, the purported uncanny valley effect in avatars was observed in both children with ASD and TD, suggesting that this factor should be considered when developing social stimuli using avatar forms. Further research is needed to define the boundary between realism and cartoons to better design stimuli that can enhance our understanding of how individuals with ASD explore their social environment. Based on these results, we can now conclude that our Cartoon task involved stimuli that were not explored differently from realistic social stimuli. Consequently, we can dismiss this hypothesis and effectively support the hypothesis that the task was overly simple for the assessed children, but potentially more suitable for younger children.

In summary, our eye-tracking studies have provided valuable insights into the atypical exploration of social stimuli in autism, enriching the existing body of eye-tracking literature. Various factors, including the presence of social interactions and non-social stimuli related to the restricted interests of autistic children, appear to modulate this atypical exploration. Our research emphasizes the substantial heterogeneity in visual exploration, challenging the social motivation hypothesis that assumes a universally shared atypical exploration among individuals with ASD. Nonetheless, our studies consistently reveal that children whose visual exploration patterns more closely resemble typical patterns demonstrate improved cognitive, adaptive abilities, as well as reduced social symptoms. This finding once again underscores the critical role of social attention during early childhood development and suggests a close relationship between atypical social attention and symptoms.

## 3.3 Enhancing social attention to improve intervention outcomes: a realistic challenge?

As emphasized throughout this work, children with ASD display atypical social attention, primarily assessed using eye-tracking. My personal studies have also demonstrated that this attention appears to be significantly influenced by the presence of social interaction, social complexity, and the presence of highly interesting non-social stimuli for children with ASD. We also discovered that social orientation was not among the predictors of progress but seemed to modulate the response to intervention within groups. Based on all the insights I have gathered throughout my work; I designed a clinical study which aimed at enhancing social attention to potentially increase the response to intervention by providing children with stronger foundational skills for their subsequent learning. In this section, we will discuss the preliminary results from the ongoing RCT, bearing in mind that we currently have a limited sample size of only seven children who completed the RCT at the time of writing.

It is interesting to note that children from the REM group paid more attention to all the tasks compared to children from the SHAM group, who sometimes did not even surpass the 50% threshold of time spent on screen required. Given that the only difference between the tasks is the contingency, it seems that contingent tasks are generally more appealing to the children. This initial finding is worth considering, especially when designing future eye-tracking tasks for very young children. Indeed, although eye-tracking is a relatively engaging tool, the tasks proposed are not always enjoyable, and it can be challenging to maintain the attention of a hyperactive child on a task that presents a static face, for example. Therefore, incorporating a contingency component might be an effective way to improve the engagement in populations with more limited attention spans. Interestingly, we observed this effect even in Task 1, which only included music as the contingent reward. This suggests that minimal feedback was sufficient to enhance attention enough. Consequently, it could be possible to design paradigms where we would display audio cues for individuals who lose interest in the screen without altering the visual exploration of the task. Overall, this result emphasizes the importance of contingency in social relationships, as a contingent response seems to maintain social motivation, translated here by extended visual exploration.

Regarding Task 1, the results currently appear to be heading in the right direction. Indeed, we observe that children in the REM group spend more time on faces compared to those in the SHAM group. Although this is partly due to a child with a relatively high average in the REM group at present, the results indicate that children in the REM group are progressively increasing their time spent on faces expressing positive emotions (e.g., smiles). Conversely, there is a trend in the SHAM group to spend more time on objects, particularly high-interest objects (HIAs). In summary, children in the REM group appear to invest more time in positive emotional faces and neglect HIAs, while the opposite is observed in the SHAM group. It is worth noting here that positive emotional faces are favored, and the increased time spent in the REM group is focused on them and not much on neutral faces. It is frequently reported in the literature that faces with positive expressions have an advantage in both emotion recognition speed and attention time overall, which could explain this result (Calvo & Nummenmaa, 2008; Juth et al., 2005). Additionally, we could also hypothesize that the fact that the music played featured joyful sounds might reinforce the association between happy faces and the reward. Thus far, the results appear to be consistent with the study that inspired this design, which paired positive music (chosen by the participant) with faces (neutral and positive) to reduce anxiety symptoms (Lazarov et al., 2017).
From a more personal perspective, I assumed that this design would be the least attention-grabbing for children, and I consistently presented it first. However, in practice, only one child during a session did not exceed the 50% attention threshold, a situation more common in other tasks that seemed to me more "simple" or at least more engaging for children. In my opinion, this phenomenon is primarily due to the contingency and the music that children seem to enjoy greatly, as well as the presence of the HIAs that appear to sustain children's attention even during the most challenging moments. The large number of items to explore also seems to be a significant help to the children, encouraging them to actively explore during the presentation time.

Concerning Task 2, the results also seem to point in the right direction concerning the speed of reactivation, notably by the progressive decrease of the latter over time. In other words, children appear to look at the avatar's face faster throughout sessions, suggesting a learning of the contingency between looking at the face and resuming the cartoon. Yet, it is interesting to note that this pattern is observed in both groups. Thus, having the avatar speaking every time the cartoon is resuming to signify that he has control over the cartoon, seems already sufficient to lean the association between the pauses and the avatar. On the other hand, it seems that the percentages of time spent on the face and the penguins are the opposite of what was expected, with a greater proportion of time spent on the face in the SHAM group compared to the children from the REM group. This is currently led by the presence of an "outlier" in the SHAM group, who got stuck on the avatar's face during the last sessions. From a personal point of view, this result comes as little surprise to me given the symptoms of this child, who is relatively slow and frequently gets fixated on topics, with repeated questions that routinely recurred between sessions. It is therefore unsurprising that this child may exhibit a sticky visual exploration pattern, which is something frequently described in the literature and associated with more symptoms (Elsabbagh et al., 2012; Sacrey et al., 2013, 2014; Thorup et al., 2016). Results might take this behavior into consideration and exclude children stuck on the face before the pauses as they are skewing the data towards decreased activation time and biasing results.
Nonetheless, an alternative explanation regarding the increased time spent on the face in the SHAM group could be that the non-contingency of the latter would encourage children to look at it more frequently as they might not fully grasp when it will pause and resume the cartoon. In this case children, children in the REM group might look at it during appropriate moments only and focus on the cartoon when it is playing. From this perspective, learning about contingency and knowing that they have some control over the break time would allow the REM group to be able to follow the cartoon while the children in the SHAM group are missing what is relevant by looking at the avatar.

Regarding Task 3, our results also align with the expected direction. Indeed, children from the REM group exhibit a higher percentage of time spent on the social side of the screen compared to the SHAM group. In addition, it seems that children in the SHAM group tend to decrease their time spent on social stimuli, while REM children maintain or even increase their engagement with them. Once again, contingency appears to sustain the children's interest in the task, and the control exerted enhances the social motivation of the REM group. On the other hand, it seems that the speed of orientation towards the social task does not significantly differ between groups. It may be too early to try to interpret the results regarding orientation speed. As of now, we can only conclude that social prioritization is equivalent between groups.
It is surprising to see the large difference between groups on this task, especially given the static, relatively repetitive, non-social stimuli. From my personal observation, I believe that children are very sensitive to the music stopping when the social stimuli are no longer being looked at (as in Task 1) and therefore quickly return to them, restarting the process. In contrast, children in the SHAM group, with no

opportunity to restart, disengage more easily from the social stimuli when they turn off and generally shift to explore the non-social stimuli. In any case, this result once again provides a good illustration of how gaze-contingency contributes to maintaining interest in a stimulus.

Concerning Task 4, it appears that the initial results are once again consistent with our hypotheses. We observe that the children in the REM group spend more time in the AOIs derived from the visual exploration of TD children. Considering that the scene is masked once they leave these AOIs, it is not surprising to see that they spend more time within them. However, this result informs us that the mask seems to effectively redirect children's attention towards typical exploration, and that they do not persist in watching the shadowed areas. On the other hand, as expected and previously evidenced by studies from our group (Jan et al., 2019), children with ASD from the SHAM group, without any cues, quickly deviate from a typical visual exploration of the cartoon. In addition, they also seem to spend less and less time in typical areas over the sessions, which might reflect a global habituation/disinterest in the non-contingent task. Overall, it is interesting to note that the mask effectively redirects attention. Moreover, it appears to do so in a rather playful way, as the children do not complain about it even though some make comments about it. Further analysis on this task could examine the number of times the mask is activated, which might reflect a tendency to drift from the norm within a session. Comparing this number over time might give us an idea of whether exploration is "normalizing" in the REM group of children. It would also be interesting to imagine this type of task, coupled with EEG tests, to investigate if the reorientation of attention leads to the activation of typical brain areas as well, and thus somehow compensates for the atypical brain activation globally reported.

Regarding the non-contingent eye-tracking tasks utilized as outcome measures, no significant differences are currently observed among them. However, it appears that children from the REM group tend to increase their time spent on social aspects in the Bio vs. Non-Bio task, which aligns with the expected outcome. The other tasks, such as the Direct Speech and Cartoon tasks, are more challenging to interpret, given that the percentage of time spent on social/face aspects is already relatively high at baseline for both tasks. To determine if the effects of remediation can be generalized, additional participants will be necessary. Nonetheless, the results are promising. As for the questionnaire outcomes, there are currently no significant findings nor any discernible trend, whether in the SRS, the progress questionnaire, or the ECAS. Further participants will be required to draw any conclusions about the parents' perceptions of the intervention's effects.

In conclusion, it is currently challenging to determine whether the remediation will yield positive results and effectively enhance social attention in children with ASD. However, the overall outcomes of the various tasks are heading in the right direction, which serves as an encouraging initial step. Numerous phases still need to be completed before the potential effects of increased social attention can be observed, if any. It is likely that the results will once again underscore the vast heterogeneity of autism, highlighting profiles that are more responsive to the intervention. Bearing in mind that this study is a pilot, it is crucial to recognize its role in identifying profiles of children who may benefit more extensively from this type of social attention booster.

## 3.4 Future directions

A logical next step involves completing the RCT. Following this, numerous potential directions can be pursued. For instance, the RCT could lead to a follow-up study with the same children to explore whether the effects are sustained over time and if any benefits arise from the intervention's outcome in relation to increased social orienting. Another possibility is to connect the observed changes over time with fMRI data, examining whether children who improved in specific tasks or displayed overall improvement exhibit reduced alterations in social brain regions. Furthermore, we could explore the possibility of offering this intervention to children participating in ESDM therapy, evaluating whether their progress following the intervention are accelerated compared to those who have not experienced the eye-tracking social attention booster. If proven effective, this would bolster the idea that children with heightened social orientation make faster progress, and that we can optimize this innate social orienting to maximize outcomes.

During my thesis, I also created other tasks that are not discussed within this work since data collection was in progress at the time of writing. These tasks have been thought in the same logic as this thesis and are thus completing it. Their completion and publication are therefore part of the next steps. One of these tasks was a gaze-contingent task which was designed to measure at which speed children with ASD grasp gaze-contingent paradigms and if there is any difference when we use social or non-social stimuli (see Fig.31). We used cars as stimuli, considering that they frequently appear among the restricted interests associated with ASD (Klin et al., 2007). Given the pronounced attentional bias towards objects related to these restricted interests in the visual exploration of individuals with ASD, we anticipate a strong orientation towards such objects. This should in turn be accompanied by rapid learning of the contingency in this specific condition, as opposed to the social condition, which is expected to deviate substantially from that of TD children. This task could provide valuable insights into the cognitive processing and attentional mechanisms of children with ASD, specifically in the context of social vs non-social stimuli. This task could also yield valuable insights into the disparities in learning rates between TD children and those with ASD.

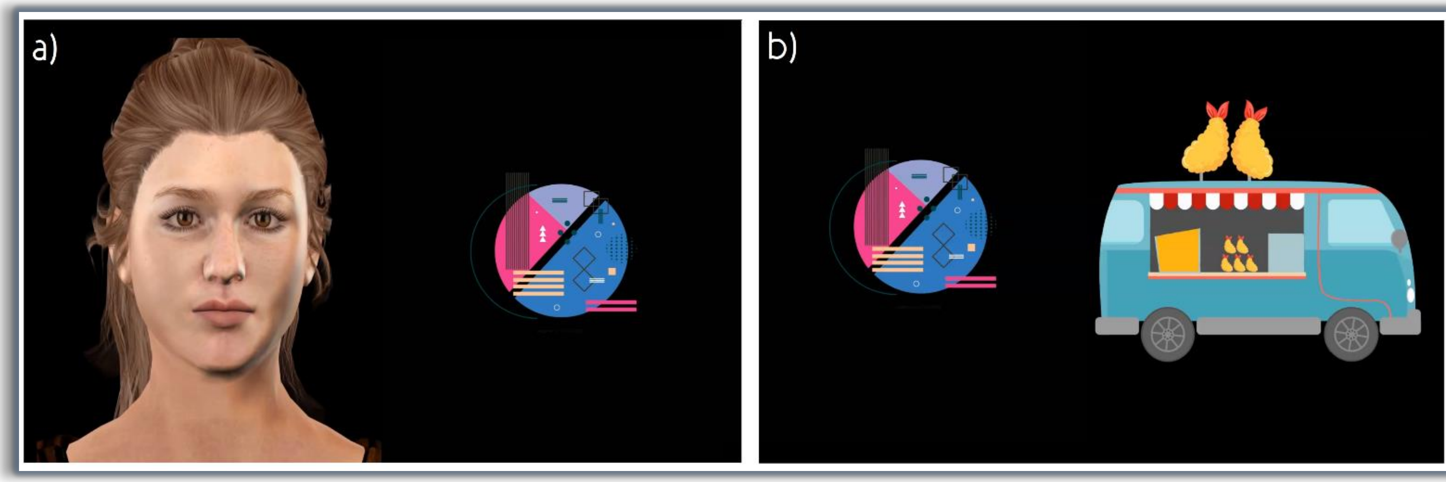


Figure 31 – Sample stimuli from the social vs non-social gaze-contingent task a) Social version of the gaze-contingent task b) Non-social version of the gaze-contingent task

The last task I developed represents a shift in my work, as it focuses less on social motivation theory and more on investigating fundamental attention mechanisms underpinning ASD symptoms. This most recent task was developed as an alternative to preferential gaze paradigms and was inspired from Avni et al., (2019). The postulate here is that children with ASD exhibit significant idiosyncrasies when viewing screens, meaning they don't look at the same areas of the screen as a typical person would while watching the same scene, due to neurodivergent attentional mechanisms. The primary objective of this final task was to have children watch a movie clip from Charlie Chaplin's "The Kid," once in a clear format and another time using a gaze-contingent masked approach (see Fig.32). Here again implementing a gaze-contingent mask was done to encourage children to thoroughly explore the scene and ensure that no processing occurred in the peripheral visual field. The overarching hypothesis for this task is that children with higher idiosyncrasy scores would display more severe symptoms. Additionally, I anticipate high-risk children to show greater idiosyncrasy if they later develop ASD symptoms. Idiosyncrasy could therefore be a more reliable biomarker of ASD compared to geometric preference, as the latter is observed only in certain subgroups of children with ASD. Indeed, while the preference for geometric patterns in preference tasks is undeniably specific to

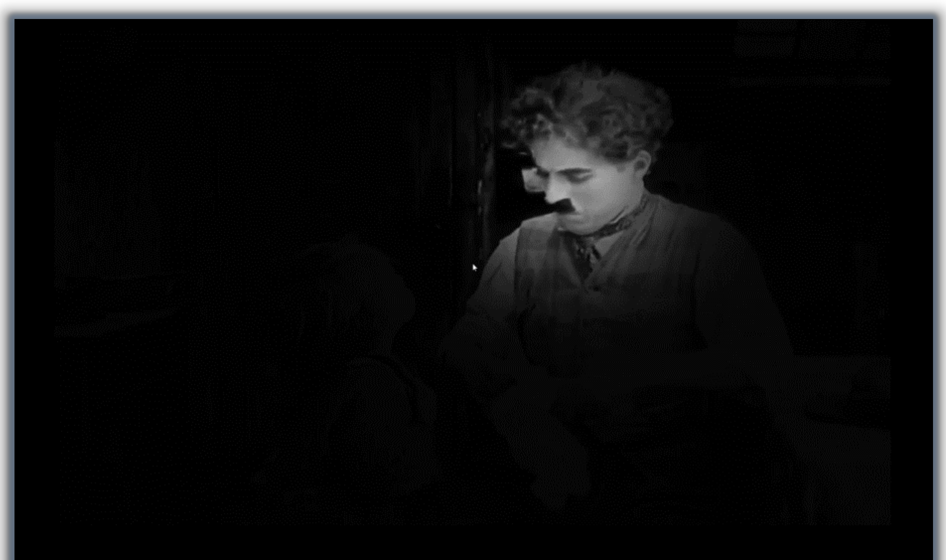

Figure 32 – Screenshot from the Chaplin masked task

ASD, it is not prevalent enough to be considered a robust biomarker for autism. Conversely, I believe that atypical exploration parameters based on attentional processes might serve as more powerful biomarkers for autism.

Lastly, I believe it would be worth to re-examine the results from the Cartoon task, this time focusing solely on at-risk children. Indeed, we will soon have enough children for whom we have collected longitudinal data, having seen this task when they were younger and for whom we now have enough information to determine a diagnosis. This could shed light on the potential altered social preference among children at-risk and clarify our understanding of previous findings.

# 4 – Conclusion

Throughout my research, I have sought to shed light on autism's heterogeneity and the varying progress of children even when they undergo the same intervention. I was able to confirm that early intervention is essential for children to exhibit optimal progress. While often acknowledged that children with better cognitive profile benefit more from interventions, I demonstrated that it is possible even for children with very low cognitive levels to make tremendous gains. I argued that the intensity of an intervention should depend on the child and their needs, rather than being uniformly applied across an entire program. Additionally, I found that children who were paying more attention to their social environment tended to progress more rapidly, which will later lead me to consider eye-tracking-based remediation. Lastly, I was able to show that, despite very different developmental patterns within the same intervention, it is possible to predict whether a child will have progressed or not at the end of an intervention by observing their early results. I hope that all these findings contribute to a better understanding of autism's heterogeneity and to the development of tailored interventions better suited to the needs of children.

Assuming that social attention, our ability to observe our social environment, is crucial in the development of early skills, I investigated how children with autism visually explore their social environment, the extent of variability among them, and the factors that influence their social attention. My studies confirmed that there are indeed significant differences among children with ASD, with some exhibiting typical gaze patterns and others displaying atypical exploration. I also showed that children who deviate the most from the norm in their gaze patterns are those with more severe symptoms, reinforcing the idea that these factors are potentially directly related. I created new designs that, although not always yielding the expected results, encouraged further questioning. For instance, I was able to demonstrate that children look at cartoons and real faces in the same way, which was not previously investigated, and may help in the development of future paradigms.

Finally, based on all these findings, I attempted to enhance children’s social attention skills before intervention to enable faster progress subsequently. To do so, I created a unique clinical trial using gaze-contingent eye-tracking paradigms. The results are currently encouraging, and I hope they will confirm that it is possible to enhance social attention. This could help many children benefit more fully from the interventions provided.

There is still much work to be done in this field, and future directions are as diverse as the manifestations of autism, which is what makes the field so fascinating.

# 5 – References


Allen, G., & Courchesne, E. (2001). Attention function and dysfunction in autism. *Frontiers in Bioscience: A Journal and Virtual Library*, *6*, D105-119. https://doi.org/10.2741/allen

Amaral, D. G., & Nordahl, C. W. (2022). Amygdala Involvement in Autism: Early Postnatal Changes, But What Are the Behavioral Consequences? *The American Journal of Psychiatry*, *179*(8), 522–524. https://doi.org/10.1176/appi.ajp.20220509

American Psychiatric Association (Ed.). (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed). American Psychiatric Association.

Anderson, D. K., Lord, C., Risi, S., DiLavore, P. S., Shulman, C., Thurm, A., Welch, K., & Pickles, A. (2007). Patterns of growth in verbal abilities among children with autism spectrum disorder. *Journal of Consulting and Clinical Psychology*, *75*(4), 594–604. https://doi.org/10.1037/0022-006X.75.4.594

Andersson, R., Larsson, L., Holmqvist, K., Stridh, M., & Nyström, M. (2017). One algorithm to rule them all? An evaluation and discussion of ten eye movement event-detection algorithms. *Behavior Research Methods*, *49*(2), 616–637. https://doi.org/10.3758/s13428-016-0738-9

Antshel, K. M., & Russo, N. (2019). Autism Spectrum Disorders and ADHD: Overlapping Phenomenology, Diagnostic Issues, and Treatment Considerations. *Current Psychiatry Reports*, *21*(5), 34. https://doi.org/10.1007/s11920-019-1020-5

Athari, P., Dey, R., & Rvachew, S. (2021). Vocal imitation between mothers and infants. *Infant Behavior & Development*, *63*, 101531. https://doi.org/10.1016/j.infbeh.2021.101531

Atherton, G., & Cross, L. (2021). Reading the mind in cartoon eyes: Comparing human versus cartoon emotion recognition in those with high and low levels of autistic traits. *Psychological Reports*, 33294120988135. https://doi.org/10.1177/0033294120988135

Atmaca, M., Yildirim, H., Yilmaz, S., Caglar, N., Mermi, O., Korkmaz, S., Akaslan, U., Gurok, M. G., Kekilli, Y., & Turkcapar, H. (2018). Orbito-frontal cortex and thalamus volumes in the patients with obsessive-compulsive disorder before and after cognitive behavioral therapy. *International Journal of Psychiatry in Medicine*, *53*(4), 243–255. https://doi.org/10.1177/0091217415621038

Avni, I., Meiri, G., Bar-Sinai, A., Reboh, D., Manelis, L., Flusser, H., Michaelovski, A., Menashe, I., & Dinstein, I. (2019). Children with autism observe social interactions in an idiosyncratic manner. *Autism Research: Official Journal of the International Society for Autism Research*. https://doi.org/10.1002/aur.2234

Ayzenberg, V., & Behrmann, M. (2022). The Dorsal Visual Pathway Represents Object-Centered Spatial Relations for Object Recognition. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *42*(23), 4693–4710. https://doi.org/10.1523/JNEUROSCI.2257-21.2022

Bachevalier, J., & Loveland, K. A. (2006). The orbitofrontal-amygdala circuit and self-regulation of social-emotional behavior in autism. *Neuroscience and Biobehavioral Reviews*, *30*(1), 97–117. https://doi.org/10.1016/j.neubiorev.2005.07.002

Baron-Cohen, S. (2002). The extreme male brain theory of autism. *Trends in Cognitive Sciences*, *6*(6), 248–254. https://doi.org/10.1016/s1364-6613(02)01904-6

Baron-Cohen, S., Ring, H. A., Wheelwright, S., Bullmore, E. T., Brammer, M. J., Simmons, A., & Williams, S. C. R. (n.d.). Social intelligence in the normal and autistic brain: An fMRI study. *European Journal of Neuroscience*, *11*(6), 1891–1898. https://doi.org/10.1046/j.1460-9568.1999.00621.x

Barton, R. A., & Dunbar, R. I. M. (1997). Evolution of the social brain. In A. Whiten & R. W. Byrne (Eds.), *Machiavellian Intelligence II: Extensions and Evaluations* (pp. 240–263). Cambridge University Press. https://doi.org/10.1017/CBO9780511525636.010

Basso, M. A., Bickford, M. E., & Cang, J. (2021). Unraveling circuits of visual perception and cognition through the superior colliculus. *Neuron*, *109*(6), 918–937. https://doi.org/10.1016/j.neuron.2021.01.013

Baxter, M. G., & Murray, E. A. (2002). The amygdala and reward. *Nature Reviews. Neuroscience*, *3*(7), 563–573. https://doi.org/10.1038/nrn875

Bejarano-Martín, Á., Canal-Bedia, R., Magán-Maganto, M., Fernández-Álvarez, C., Cilleros-Martín, M. V., Sánchez-Gómez, M. C., García-Primo, P., Rose-Sweeney, M., Boilson, A., Linertová, R., Roeyers, H., Van der Paelt, S., Schendel, D., Warberg, C., Cramer, S., Narzisi, A., Muratori, F., Scattoni, M. L., Moilanen, I., … Posada de la Paz, M. (2020). Early Detection, Diagnosis and Intervention Services for Young Children with Autism Spectrum Disorder in the European Union (ASDEU): Family and Professional Perspectives. *Journal of Autism and Developmental Disorders*, *50*(9), 3380–3394. https://doi.org/10.1007/s10803-019-04253-0

Berenguer, C., Roselló, B., Colomer, C., Baixauli, I., & Miranda, A. (2018). Children with autism and attention deficit hyperactivity disorder. Relationships between symptoms and executive function, theory of mind, and behavioral problems. *Research in Developmental Disabilities*, *83*, 260–269. https://doi.org/10.1016/j.ridd.2018.10.001

Bi, Y., Wang, X., & Caramazza, A. (2016). Object Domain and Modality in the Ventral Visual Pathway. *Trends in Cognitive Sciences*, *20*(4), 282–290. https://doi.org/10.1016/j.tics.2016.02.002

Blignaut, P. (2009). Fixation identification: The optimum threshold for a dispersion algorithm. *Attention, Perception, & Psychophysics*, *71*(4), 881–895. https://doi.org/10.3758/APP.71.4.881

Bracci, S., Ritchie, J. B., & de Beeck, H. O. (2017). On the partnership between neural representations of object categories and visual features in the ventral visual pathway. *Neuropsychologia*, *105*, 153–164. https://doi.org/10.1016/j.neuropsychologia.2017.06.010

Brandt, J. S., Cruz Ithier, M. A., Rosen, T., & Ashkinadze, E. (2019). Advanced paternal age, infertility, and reproductive risks: A review of the literature. *Prenatal Diagnosis*, *39*(2), 81–87. https://doi.org/10.1002/pd.5402

Bray, I., Gunnell, D., & Davey Smith, G. (2006). Advanced paternal age: How old is too old? *Journal of Epidemiology and Community Health*, *60*(10), 851–853. https://doi.org/10.1136/jech.2005.045179

Brieber, S., Neufang, S., Bruning, N., Kamp-Becker, I., Remschmidt, H., Herpertz-Dahlmann, B., Fink,

G. R., & Konrad, K. (2007). Structural brain abnormalities in adolescents with autism spectrum disorder and patients with attention deficit/hyperactivity disorder. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *48*(12), 1251–1258. https://doi.org/10.1111/j.1469-7610.2007.01799.x

Brooks, R., & Meltzoff, A. N. (2005). The development of gaze following and its relation to language. *Developmental Science*, *8*(6), 535–543. https://doi.org/10.1111/j.1467-7687.2005.00445.x

Brothers, L. (1990). The social brain: A project for integrating primate behavior and neuropsychology in a new domain. *Concepts in Neuroscience*, *1*, 27–51.

Buswell, G. T. (1937). How adults read. *University of Chicago*, *45*.

Calvo, M. G., & Nummenmaa, L. (2008). Detection of emotional faces: Salient physical features guide effective visual search. *Journal of Experimental Psychology: General*, *137*, 471–494. https://doi.org/10.1037/a0012771

Cannon, J., O'Brien, A. M., Bungert, L., & Sinha, P. (2021). Prediction in Autism Spectrum Disorder: A Systematic Review of Empirical Evidence. *Autism Research : Official Journal of the International Society for Autism Research*, *14*(4), 604–630. https://doi.org/10.1002/aur.2482

Carelli, L., Solca, F., Tagini, S., Torre, S., Verde, F., Ticozzi, N., Ferrucci, R., Pravettoni, G., Aiello, E. N., Silani, V., & Poletti, B. (2022). Gaze-Contingent Eye-Tracking Training in Brain Disorders: A Systematic Review. *Brain Sciences*, *12*(7), Article 7. https://doi.org/10.3390/brainsci12070931

Carette, R., Elbattah, M., Cilia, F., Dequen, G., Guérin, J.-L., & Bosche, J. (2020). *Learning to Predict Autism Spectrum Disorder based on the Visual Patterns of Eye-tracking Scanpaths*. 103–112. http://www.scitepress.org/DigitalLibrary/Link.aspx?doi=10.5220/0007402601030112

Carpenter, M., Nagell, K., Tomasello, M., Butterworth, G., & Moore, C. (1998). Social Cognition, Joint Attention, and Communicative Competence from 9 to 15 Months of Age. *Monographs of the Society for Research in Child Development*, *63*(4), i–174. https://doi.org/10.2307/1166214

Carruthers, S., Pickles, A., Slonims, V., Howlin, P., & Charman, T. (2020). Beyond intervention into daily life: A systematic review of generalisation following social communication interventions for young children with autism. *Autism Research: Official Journal of the International Society for Autism Research*, *13*(4), 506–522. https://doi.org/10.1002/aur.2264

Carter, C. J., & Blizard, R. A. (2016). Autism genes are selectively targeted by environmental pollutants including pesticides, heavy metals, bisphenol A, phthalates and many others in food, cosmetics or household products. *Neurochemistry International*, S0197-0186(16)30197-8. https://doi.org/10.1016/j.neuint.2016.10.011

Catani, M., Dell'Acqua, F., Budisavljevic, S., Howells, H., Thiebaut de Schotten, M., Froudist-Walsh, S., D'Anna, L., Thompson, A., Sandrone, S., Bullmore, E. T., Suckling, J., Baron-Cohen, S., Lombardo, M. V., Wheelwright, S. J., Chakrabarti, B., Lai, M.-C., Ruigrok, A. N. V., Leemans, A., Ecker, C., … Murphy, D. G. M. (2016). Frontal networks in adults with autism spectrum disorder. *Brain: A Journal of Neurology*, *139*(Pt 2), 616–630. https://doi.org/10.1093/brain/awv351

Chawarska, K., Volkmar, F., & Klin, A. (2010). Limited attentional bias for faces in toddlers with autism spectrum disorders. *Archives of General Psychiatry*, *67*(2), 178–185. https://doi.org/10.1001/archgenpsychiatry.2009.194

Cheroni, C., Caporale, N., & Testa, G. (2020). Autism spectrum disorder at the crossroad between genes and environment: Contributions, convergences, and interactions in ASD developmental pathophysiology. *Molecular Autism*, *11*(1), 69. https://doi.org/10.1186/s13229-020-00370-1

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E. S., & Schultz, R. T. (2012). The Social Motivation Theory of Autism. *Trends in Cognitive Sciences*, *16*(4), 231–239. https://doi.org/10.1016/j.tics.2012.02.007

Chevallier, C., Parish-Morris, J., McVey, A., Rump, K. M., Sasson, N. J., Herrington, J. D., & Schultz, R. T. (2015). Measuring social attention and motivation in autism spectrum disorder using eye-tracking: Stimulus type matters. *Autism Research*, *8*(5), 620–628. https://doi.org/10.1002/aur.1479

Chevallier, C., Parish-Morris, J., McVey, A., Rump, K. M., Sasson, N. J., Herrington, J. D., & Schultz, R. T. (2015). Measuring social attention and motivation in autism spectrum disorder using eye-tracking: Stimulus type matters. *Autism Research*, *8*(5), 620–628. https://doi.org/10.1002/aur.1479

Collins, W. A., & Gunnar, M. R. (1990). Social and personality development. *Annual Review of Psychology*, *41*, 387–416. https://doi.org/10.1146/annurev.ps.41.020190.002131

Courchesne, E., & Pierce, K. (2005). Why the frontal cortex in autism might be talking only to itself: Local over-connectivity but long-distance disconnection. *Current Opinion in Neurobiology*, *15*(2), 225–230. https://doi.org/10.1016/j.conb.2005.03.001

Crucitti, J., Hyde, C., Enticott, P. G., & Stokes, M. A. (2022). A systematic review of frontal lobe volume in autism spectrum disorder revealing distinct trajectories. *Journal of Integrative Neuroscience*, *21*(2), 57. https://doi.org/10.31083/j.jin2102057

Dapretto, M., Davies, M. S., Pfeifer, J. H., Scott, A. A., Sigman, M., Bookheimer, S. Y., & Iacoboni, M. (2006). Understanding emotions in others: Mirror neuron dysfunction in children with autism spectrum disorders. *Nature Neuroscience*, *9*(1), Article 1. https://doi.org/10.1038/nn1611

Davis, J., Redshaw, J., Suddendorf, T., Nielsen, M., Kennedy-Costantini, S., Oostenbroek, J., & Slaughter, V. (2021). Does Neonatal Imitation Exist? Insights From a Meta-Analysis of 336 Effect Sizes. *Perspectives on Psychological Science*, *16*(6), 1373–1397. https://doi.org/10.1177/1745691620959834

Dawson, G. (2008). Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. *Development and Psychopathology*, *20*(3), 775–803. https://doi.org/10.1017/S0954579408000370

Dawson, G., Meltzoff, A. N., Osterling, J., Rinaldi, J., & Brown, E. (1998). Children with autism fail to orient to naturally occurring social stimuli. *Journal of Autism and Developmental Disorders*, *28*(6), 479–485. https://doi.org/10.1023/a:1026043926488

Dawson, G., Rogers, SJ., Munson, J., Smith, M., Winter, J., Greenson, J., Donaldson, A., & Varley, J. (2010). Randomized, Controlled Trial of an Intervention for Toddlers With Autism: The Early Start Denver Model. *Pediatrics*, *125*(1), e17–e23. https://doi.org/10.1542/peds.2009-0958

Dawson, G., Toth, K., Abbott, R., Osterling, J., Munson, J., Estes, A., & Liaw, J. (2004). Early social attention impairments in autism: Social orienting, joint attention, and attention to distress. *Developmental Psychology*, *40*(2), 271–283. https://doi.org/10.1037/0012-1649.40.2.271

Dean, M., Harwood, R., & Kasari, C. (2017). The art of camouflage: Gender differences in the social behaviors of girls and boys with autism spectrum disorder. *Autism*, *21*(6), 678–689. https://doi.org/10.1177/1362361316671845

D'Elia, L., Valeri, G., Sonnino, F., Fontana, I., Mammone, A., & Vicari, S. (2014). A Longitudinal Study of the Teacch Program in Different Settings: The Potential Benefits of Low Intensity Intervention in Preschool Children with Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *44*(3), 615–626. https://doi.org/10.1007/s10803-013-1911-y

Donald, M. (1991). *Origins of the Modern Mind: Three Stages in the Evolution of Culture and Cognition*. Harvard University Press.

Dong, H.-Y., Feng, J.-Y., Wang, B., Shan, L., & Jia, F.-Y. (2021). Screen Time and Autism: Current Situation and Risk Factors for Screen Time Among Pre-school Children With ASD. *Frontiers in Psychiatry*, *12*, 675902. https://doi.org/10.3389/fpsyt.2021.675902

Dunaway, K. W., Islam, M. S., Coulson, R. L., Lopez, S. J., Vogel Ciernia, A., Chu, R. G., Yasui, D. H., Pessah, I. N., Lott, P., Mordaunt, C., Meguro-Horike, M., Horike, S.-I., Korf, I., & LaSalle, J. M. (2016). Cumulative Impact of Polychlorinated Biphenyl and Large Chromosomal Duplications on DNA Methylation, Chromatin, and Expression of Autism Candidate Genes. *Cell Reports*, *17*(11), 3035–3048. https://doi.org/10.1016/j.celrep.2016.11.058

Dunbar, R. I. M. (2009). The social brain hypothesis and its implications for social evolution. *Annals of Human Biology*, *36*(5), 562–572. https://doi.org/10.1080/03014460902960289

Dziobek, I., Bahnemann, M., Convit, A., & Heekeren, H. R. (2010). The role of the fusiform-amygdala system in the pathophysiology of autism. *Archives of General Psychiatry*, *67*(4), 397–405. https://doi.org/10.1001/archgenpsychiatry.2010.31

Edwards, S. G., Stephenson, L. J., Dalmaso, M., & Bayliss, A. P. (2015). Social orienting in gaze leading: A mechanism for shared attention. *Proceedings. Biological Sciences*, *282*(1812), 20151141. https://doi.org/10.1098/rspb.2015.1141

Eldevik, S., Hastings, R. P., Hughes, J. C., Jahr, E., Eikeseth, S., & Cross, S. (2009). Meta-analysis of Early Intensive Behavioral Intervention for children with autism. *Journal of Clinical Child and Adolescent Psychology*, *38*(3), 439–450. https://doi.org/10.1080/15374410902851739

Elliott, C., Sutherland, D., Gerhard, D., & Theys, C. (2022). An Evaluation of the P300 Brain-Computer Interface, EyeLink Board, and Eye-Tracking Camera as Augmentative and Alternative Communication Devices. *Journal of Speech, Language, and Hearing Research: JSLHR*, *65*(11), 4280–4290. https://doi.org/10.1044/2022_JSLHR-21-00572

Elsabbagh, M., Fernandes, J., Jane Webb, S., Dawson, G., Charman, T., & Johnson, M. H. (2013). Disengagement of Visual Attention in Infancy is Associated with Emerging Autism in Toddlerhood. *Biological Psychiatry*, *74*(3), 189–194. https://doi.org/10.1016/j.biopsych.2012.11.030

Elsabbagh, M., Mercure, E., Hudry, K., Chandler, S., Pasco, G., Charman, T., Pickles, A., Baron-Cohen, S., Bolton, P., Johnson, M. H., & BASIS Team. (2012). Infant neural sensitivity to dynamic eye gaze is associated with later emerging autism. *Current Biology: CB*, *22*(4), 338–342. https://doi.org/10.1016/j.cub.2011.12.056

Fan, S., Wang, X., Wang, X., Wei, T., & Bi, Y. (2021). Topography of Visual Features in the Human Ventral Visual Pathway. *Neuroscience Bulletin*, *37*(10), 1454–1468. https://doi.org/10.1007/s12264-021-00734-4

Farhat, L. C., Brentani, H., de Toledo, V. H. C., Shephard, E., Mattos, P., Baron-Cohen, S., Thapar, A., Casella, E., & Polanczyk, G. V. (2022). ADHD and autism symptoms in youth: A network analysis. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *63*(2), 143–151. https://doi.org/10.1111/jcpp.13436

Fariña, A., Rojek-Giffin, M., Gross, J., & De Dreu, C. K. W. (2021). Social preferences correlate with cortical thickness of the orbito-frontal cortex. *Social Cognitive and Affective Neuroscience*, *16*(11), 1191–1203. https://doi.org/10.1093/scan/nsab074

Farroni, T., Johnson, M. H., Menon, E., Zulian, L., Faraguna, D., & Csibra, G. (2005). Newborns' preference for face-relevant stimuli: Effects of contrast polarity. *Proceedings of the National Academy of Sciences*, *102*(47), 17245–17250. https://doi.org/10.1073/pnas.0502205102

Feng, S., Wang, X., Wang, Q., Fang, J., Wu, Y., Yi, L., & Wei, K. (2018). The uncanny valley effect in typically developing children and its absence in children with autism spectrum disorders. *PloS One*, *13*(11), e0206343. https://doi.org/10.1371/journal.pone.0206343

Fernell, E., Hedvall, Å., Westerlund, J., Höglund Carlsson, L., Eriksson, M., Barnevik Olsson, M., Holm, A., Norrelgen, F., Kjellmer, L., & Gillberg, C. (2011). Early intervention in 208 Swedish preschoolers with autism spectrum disorder. A prospective naturalistic study. *Research in Developmental Disabilities*, *32*(6), 2092–2101. https://doi.org/10.1016/j.ridd.2011.08.002

Fischi-Gomez, E., Bonnier, G., Ward, N., Granziera, C., & Hadjikhani, N. (2021). Ultrahigh field in vivo characterization of microstructural abnormalities in the orbitofrontal cortex and amygdala in autism. *The European Journal of Neuroscience*, *54*(6), 6229–6236. https://doi.org/10.1111/ejn.15420

Flanagan, J. E., Landa, R., Bhat, A., & Bauman, M. (2012). Head Lag in Infants at Risk for Autism: A Preliminary Study. *The American Journal of Occupational Therapy*, *66*(5), 577–585. https://doi.org/10.5014/ajot.2012.004192

Folstein, S., & Rutter, M. (1977). Infantile autism: A genetic study of 21 twin pairs. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *18*(4), 297–321. https://doi.org/10.1111/j.1469-7610.1977.tb00443.x

Franchini, M., Glaser, B., Wood de Wilde, H., Gentaz, E., Eliez, S., & Schaer, M. (2017). Social orienting and joint attention in preschoolers with autism spectrum disorders. *PloS One*, *12*(6), e0178859. https://doi.org/10.1371/journal.pone.0178859

Franchini, M., Wood de Wilde, H., Glaser, B., Gentaz, E., Eliez, S., & Schaer, M. (2016). Brief Report: A Preference for Biological Motion Predicts a Reduction in Symptom Severity 1 Year Later in

Preschoolers with Autism Spectrum Disorders. *Frontiers in Psychiatry*, *7*. https://doi.org/10.3389/fpsyt.2016.00143

Frank, M. C., Vul, E., & Johnson, S. P. (2009). Development of infants' attention to faces during the first year. *Cognition*, *110*(2), 160–170. https://doi.org/10.1016/j.cognition.2008.11.010

Frazier, T. W., Strauss, M., Klingemier, E. W., Zetzer, E. E., Hardan, A. Y., Eng, C., & Youngstrom, E. A. (2017). A Meta-Analysis of Gaze Differences to Social and Nonsocial Information Between Individuals With and Without Autism. *Journal of the American Academy of Child and Adolescent Psychiatry*, *56*(7), 546–555. https://doi.org/10.1016/j.jaac.2017.05.005

Freud, E., Plaut, D. C., & Behrmann, M. (2016). "What" Is Happening in the Dorsal Visual Pathway. *Trends in Cognitive Sciences*, *20*(10), 773–784. https://doi.org/10.1016/j.tics.2016.08.003

Frick, J. E., Colombo, J., & Saxon, T. F. (1999). Individual and developmental differences in disengagement of fixation in early infancy. *Child Development*, *70*(3), 537–548. https://doi.org/10.1111/1467-8624.00039

Friston, K. J., Lawson, R., & Frith, C. D. (2013). On hyperpriors and hypopriors: Comment on Pellicano and Burr. *Trends in Cognitive Sciences*, *17*(1), 1. https://doi.org/10.1016/j.tics.2012.11.003

Frost, K. M., Brian, J., Gengoux, G. W., Hardan, A., Rieth, S. R., Stahmer, A., & Ingersoll, B. (2020). Identifying and measuring the common elements of naturalistic developmental behavioral interventions for autism spectrum disorder: Development of the NDBI-Fi. *Autism*, *24*(8), 2285–2297. https://doi.org/10.1177/1362361320944011

Fuentes, J., Hervás, A., Howlin, P., & (ESCAP ASD Working Party). (2021). ESCAP practice guidance for autism: A summary of evidence-based recommendations for diagnosis and treatment. *European Child & Adolescent Psychiatry*, *30*(6), 961–984. https://doi.org/10.1007/s00787-020-01587-4

Gabis, L. V., Attia, O. L., Goldman, M., Barak, N., Tefera, P., Shefer, S., Shaham, M., & Lerman-Sagie, T. (2022). The myth of vaccination and autism spectrum. *European Journal of Paediatric Neurology*, *36*, 151–158. https://doi.org/10.1016/j.ejpn.2021.12.011

Gale, C. M., Eikeseth, S., & Klintwall, L. (2019). Children with Autism show Atypical Preference for Non-social Stimuli. *Scientific Reports*, *9*, 10355. https://doi.org/10.1038/s41598-019-46705-8

Gallagher, M., & Chiba, A. A. (1996). The amygdala and emotion. *Current Opinion in Neurobiology*, *6*(2), 221–227. https://doi.org/10.1016/s0959-4388(96)80076-6

Gallivan, J. P., & Goodale, M. A. (2018). The dorsal "action" pathway. *Handbook of Clinical Neurology*, *151*, 449–466. https://doi.org/10.1016/B978-0-444-63622-5.00023-1

Garaas, T. W., Nieuwenhuis, T., & Pomplun, M. (2008). A gaze-contingent paradigm for studying continuous saccadic adaptation. *Journal of Neuroscience Methods*, *168*(2), 334–340. https://doi.org/10.1016/j.jneumeth.2007.10.022

Goodrich, A. J., Volk, H. E., Tancredi, D. J., McConnell, R., Lurmann, F. W., Hansen, R. L., & Schmidt, R. J. (2018). Joint effects of prenatal air pollutant exposure and maternal folic acid supplementation on risk of autism spectrum disorder. *Autism Research*, *11*(1), 69–80. https://doi.org/10.1002/aur.1885

Goold, S., Murphy, M. J., Goodale, M. A., Crewther, S. G., & Laycock, R. (2022). Faster social attention disengagement in individuals with higher autism traits. *Journal of Clinical and Experimental Neuropsychology*, *44*(10), 755–767. https://doi.org/10.1080/13803395.2023.2167943

Gotham, K., Pickles, A., & Lord, C. (2009). Standardizing ADOS scores for a measure of severity in autism spectrum disorders. *Journal of Autism and Developmental Disorders*, *39*(5), 693–705. https://doi.org/10.1007/s10803-008-0674-3

Granpeesheh, D., Dixon, D. R., Tarbox, J., Kaplan, A. M., & Wilke, A. E. (2009). The effects of age and treatment intensity on behavioral intervention outcomes for children with autism spectrum disorders. *Research in Autism Spectrum Disorders*, *3*(4), 1014–1022. https://doi.org/10.1016/j.rasd.2009.06.007

Grelotti, D. J., Klin, A. J., Gauthier, I., Skudlarski, P., Cohen, D. J., Gore, J. C., Volkmar, F. R., & Schultz, R. T. (2005). FMRI activation of the fusiform gyrus and amygdala to cartoon characters but not to faces in a boy with autism. *Neuropsychologia*, *43*(3), 373–385.

https://doi.org/10.1016/j.neuropsychologia.2004.06.015

Guillon, Q., Hadjikhani, N., Baduel, S., & Rogé, B. (2014). Visual social attention in autism spectrum disorder: Insights from eye tracking studies. *Neuroscience & Biobehavioral Reviews*, *42*, 279–297. https://doi.org/10.1016/j.neubiorev.2014.03.013

Hampton, L. H., & Kaiser, A. P. (2016). Intervention effects on spoken-language outcomes for children with autism: A systematic review and meta-analysis. *Journal of Intellectual Disability Research: JIDR*, *60*(5), 444–463. https://doi.org/10.1111/jir.12283

Harris, S. L., & Handleman, J. S. (2000). Age and IQ at intake as predictors of placement for young children with autism: A four- to six-year follow-up. *Journal of Autism and Developmental Disorders*, *30*(2), 137–142.

Harrop, C., Jones, D., Zheng, S., Nowell, S., Schultz, R., & Parish-Morris, J. (2019). Visual attention to faces in children with autism spectrum disorder: Are there sex differences? *Molecular Autism*, *10*, 28. https://doi.org/10.1186/s13229-019-0276-2

Hein, G., & Knight, R. T. (2008). Superior temporal sulcus--It's my area: Or is it? *Journal of Cognitive Neuroscience*, *20*(12), 2125–2136. https://doi.org/10.1162/jocn.2008.20148

Heinen, K., Feredoes, E., Ruff, C. C., & Driver, J. (2017). Functional connectivity between prefrontal and parietal cortex drives visuo-spatial attention shifts. *Neuropsychologia*, *99*, 81–91. https://doi.org/10.1016/j.neuropsychologia.2017.02.024

Heinen, K., Feredoes, E., Weiskopf, N., Ruff, C. C., & Driver, J. (2014). Direct Evidence for Attention-Dependent Influences of the Frontal Eye-Fields on Feature-Responsive Visual Cortex. *Cerebral Cortex (New York, NY)*, *24*(11), 2815–2821. https://doi.org/10.1093/cercor/bht157

Hollander, E., Anagnostou, E., Chaplin, W., Esposito, K., Haznedar, M. M., Licalzi, E., Wasserman, S., Soorya, L., & Buchsbaum, M. (2005). Striatal Volume on Magnetic Resonance Imaging and Repetitive Behaviors in Autism. *Biological Psychiatry*, *58*(3), 226–232. https://doi.org/10.1016/j.biopsych.2005.03.040

Howlin, P., Magiati, I., & Charman, T. (2009). Systematic Review of Early Intensive Behavioral

Interventions for Children With Autism. *American Journal on Intellectual and Developmental Disabilities*, *114*(1), 23–41. https://doi.org/10.1352/2009.114:23-41

Hus, V., Gotham, K., & Lord, C. (2014). Standardizing ADOS domain scores: Separating severity of social affect and restricted and repetitive behaviors. *Journal of Autism and Developmental Disorders*, *44*(10), 2400–2412. https://doi.org/10.1007/s10803-012-1719-1

Hviid, A., Hansen, J. V., Frisch, M., & Melbye, M. (2019). Measles, Mumps, Rubella Vaccination and Autism: A Nationwide Cohort Study. *Annals of Internal Medicine*, *170*(8), 513–520. https://doi.org/10.7326/M18-2101

Iacoboni, M., & Dapretto, M. (2006). The mirror neuron system and the consequences of its dysfunction. *Nature Reviews Neuroscience*, *7*(12), Article 12. https://doi.org/10.1038/nrn2024

Iacoboni, M., Woods, R. P., Brass, M., Bekkering, H., Mazziotta, J. C., & Rizzolatti, G. (1999). Cortical Mechanisms of Human Imitation. *Science*, *286*(5449), 2526–2528. https://doi.org/10.1126/science.286.5449.2526

Ingersoll, B., & Lalonde, K. (2010). The impact of object and gesture imitation training on language use in children with autism. *Journal of Speech, Language, and Hearing Research : JSLHR*, *53*(4), 1040–1051. https://doi.org/10.1044/1092-4388(2009/09-0043)

Iordanescu, L., Grabowecky, M., Franconeri, S., Theeuwes, J., & Suzuki, S. (2010). Characteristic sounds make you look at target objects more quickly. *Attention, Perception & Psychophysics*, *72*(7), 1736–1741. https://doi.org/10.3758/APP.72.7.1736

Ishizuka, Y., & Yamamoto, J.-I. (2016). Contingent imitation increases verbal interaction in children with autism spectrum disorders. *Autism: The International Journal of Research and Practice*, *20*(8), 1011–1020. https://doi.org/10.1177/1362361315622856

Ismail, F. Y., Fatemi, A., & Johnston, M. V. (2017). Cerebral plasticity: Windows of opportunity in the developing brain. *European Journal of Paediatric Neurology: EJPN: Official Journal of the European Paediatric Neurology Society*, *21*(1), 23–48. https://doi.org/10.1016/j.ejpn.2016.07.007

Jan, R. K., Rihs, T. A., Kojovic, N., Sperdin, H. F., Franchini, M., Custo, A., Tomescu, M. I., Michel, C. M., & Schaer, M. (2019). Neural Processing of Dynamic Animated Social Interactions in Young Children With Autism Spectrum Disorder: A High-Density Electroencephalography Study. *Frontiers in Psychiatry*, *10*, 582. https://doi.org/10.3389/fpsyt.2019.00582

Javal, E. L. (1878). Essai sur la physiologie de la lecture. *Annales d'Ocilistique*, *80*, 97–117.

Jones, E. J. H., Venema, K., Earl, R., Lowy, R., Barnes, K., Estes, A., Dawson, G., & Webb, S. J. (2016). Reduced engagement with social stimuli in 6-month-old infants with later autism spectrum disorder: A longitudinal prospective study of infants at high familial risk. *Journal of Neurodevelopmental Disorders*, *8*, 7. https://doi.org/10.1186/s11689-016-9139-8

Jones, S. S. (2009). The development of imitation in infancy. *Philosophical Transactions of the Royal Society B: Biological Sciences*, *364*(1528), 2325–2335. https://doi.org/10.1098/rstb.2009.0045

Jones, W., & Klin, A. (2013). Attention to eyes is present but in decline in 2–6-month-old infants later diagnosed with autism. *Nature*, *504*(7480), 427. https://doi.org/10.1038/nature12715

Just, M. A., & Carpenter, P. A. (1980). A theory of reading: From eye fixations to comprehension. *Psychological Review*, *87*(4), 329–354. https://doi.org/10.1037/0033-295X.87.4.329

Just, M. A., Keller, T. A., Malave, V. L., Kana, R. K., & Varma, S. (2012). Autism as a neural systems disorder: A theory of frontal-posterior underconnectivity. *Neuroscience and Biobehavioral Reviews*, *36*(4), 1292–1313. https://doi.org/10.1016/j.neubiorev.2012.02.007

Juth, P., Lundqvist, D., Karlsson, A., & Öhman, A. (2005). Looking for Foes and Friends: Perceptual and Emotional Factors When Finding a Face in the Crowd. *Emotion*, *5*, 379–395. https://doi.org/10.1037/1528-3542.5.4.379

Kaale, A., Smith, L., & Sponheim, E. (2012). A randomized controlled trial of preschool-based joint attention intervention for children with autism. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *53*(1), 97–105. https://doi.org/10.1111/j.1469-7610.2011.02450.x

Kanner, L. (1943). Autistic disturbances of affective contact. *Nervous Child*, *2*(3), 217–250.

Kavanaugh, B. C., Gabert, T., Rhode Island Consortium for Autism Research and Treatment (RI-

CART), Jones, R. N., Sheinkopf, S. J., & Morrow, E. M. (2022). Parental age and autism severity in the Rhode Island Consortium for Autism Research and Treatment (RI-CART) study. *Autism Research: Official Journal of the International Society for Autism Research*, *15*(1), 86–92. https://doi.org/10.1002/aur.2648

Keemink, J. R., Keshavarzi-Pour, M. J., & Kelly, D. J. (2019). Infants' responses to interactive gaze-contingent faces in a novel and naturalistic eye-tracking paradigm. *Developmental Psychology*. https://doi.org/10.1037/dev0000736

Key, A. P. F., & Stone, W. L. (2012). Processing of novel and familiar faces in infants at average and high risk for autism. *Developmental Cognitive Neuroscience*, *2*(2), 244–255. https://doi.org/10.1016/j.dcn.2011.12.003

Khurana, B., & Kowler, E. (1987). Shared attentional control of smooth eye movement and perception. *Vision Research*, *27*(9), 1603–1618. https://doi.org/10.1016/0042-6989(87)90168-4

Kikuchi, Y., Senju, A., Akechi, H., Tojo, Y., Osanai, H., & Hasegawa, T. (2011). Atypical disengagement from faces and its modulation by the control of eye fixation in children with autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *41*(5), 629–645. https://doi.org/10.1007/s10803-010-1082-z

Kim, D., Volk, H., Girirajan, S., Pendergrass, S., Hall, M. A., Verma, S. S., Schmidt, R. J., Hansen, R. L., Ghosh, D., Ludena-Rodriguez, Y., Kim, K., Ritchie, M. D., Hertz-Picciotto, I., & Selleck, S. B. (2017). The joint effect of air pollution exposure and copy number variation on risk for autism. *Autism Research : Official Journal of the International Society for Autism Research*, *10*(9), 1470–1480. https://doi.org/10.1002/aur.1799

Klein, J. T., Shepherd, S. V., & Platt, M. L. (2009). Social Attention and the Brain. *Current Biology*, *19*(20), R958–R962. https://doi.org/10.1016/j.cub.2009.08.010

Klin, A., Danovitch, J., Merz-Beyus, A., & Volkmar, F. (2007). Circumscribed Interests in Higher Functioning Individuals With Autism Spectrum Disorders: An Exploratory Study. *Research and Practice for Persons with Severe Disabilities*, *32*, 89–100. https://doi.org/10.2511/rpsd.32.2.89

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual Fixation Patterns During Viewing of Naturalistic Social Situations as Predictors of Social Competence in Individuals With Autism. *Archives of General Psychiatry*, *59*(9), 809–816. https://doi.org/10.1001/archpsyc.59.9.809

Klin, A., Lin, D. J., Gorrindo, P., Ramsay, G., & Jones, W. (2009). Two-year-olds with autism orient to non-social contingencies rather than biological motion. *Nature*, *459*(7244), 257. https://doi.org/10.1038/nature07868

Koegel, L. K., Koegel, R. L., Harrower, J. K., & Carter, C. M. (1999). Pivotal Response Intervention I: Overview of Approach. *Research and Practice for Persons with Severe Disabilities*, *24*(3), 174–185. https://doi.org/10.2511/rpsd.24.3.174

Kokkinaki, T., & Kugiumutzakis, G. (2000). Basic aspects of vocal imitation in infant-parent interaction during the first 6 months. *Journal of Reproductive and Infant Psychology*, *18*(3), 173–187. https://doi.org/10.1080/713683042

Komogortsev, O. V., & Karpov, A. (2013). Automated classification and scoring of smooth pursuit eye movements in the presence of fixations and saccades. *Behavior Research Methods*, *45*(1), 203–215. https://doi.org/10.3758/s13428-012-0234-9

König, I. R., Fuchs, O., Hansen, G., Mutius, E. von, & Kopp, M. V. (2017). What is precision medicine? *European Respiratory Journal*, *50*(4). https://doi.org/10.1183/13993003.00391-2017

Kowler, E., Anderson, E., Dosher, B., & Blaser, E. (1995). The role of attention in the programming of saccades. *Vision Research*, *35*(13), 1897–1916. https://doi.org/10.1016/0042-6989(94)00279-u

Kowler, E., Rubinstein, J. F., Santos, E. M., & Wang, J. (2019). Predictive Smooth Pursuit Eye Movements. *Annual Review of Vision Science*, *5*(1), 223–246. https://doi.org/10.1146/annurev-vision-091718-014901

Kravitz, D. J., Saleem, K. S., Baker, C. I., Ungerleider, L. G., & Mishkin, M. (2013). The ventral visual pathway: An expanded neural framework for the processing of object quality. *Trends in Cognitive Sciences*, *17*(1), 26–49. https://doi.org/10.1016/j.tics.2012.10.011

Kwon, M.-K., Moore, A., Barnes, C. C., Cha, D., & Pierce, K. (2019). Typical Levels of Eye-Region Fixation in Toddlers With Autism Spectrum Disorder Across Multiple Contexts. *Journal of the American Academy of Child and Adolescent Psychiatry*, *58*(10), 1004–1015. https://doi.org/10.1016/j.jaac.2018.12.011

Lai, M.-C., Kassee, C., Besney, R., Bonato, S., Hull, L., Mandy, W., Szatmari, P., & Ameis, S. H. (2019). Prevalence of co-occurring mental health diagnoses in the autism population: A systematic review and meta-analysis. *The Lancet. Psychiatry*, *6*(10), 819–829. https://doi.org/10.1016/S2215-0366(19)30289-5

Lai, M.-C., Lombardo, M. V., Auyeung, B., Chakrabarti, B., & Baron-Cohen, S. (2015). Sex/Gender Differences and Autism: Setting the Scene for Future Research. *Journal of the American Academy of Child and Adolescent Psychiatry*, *54*(1), 11–24. https://doi.org/10.1016/j.jaac.2014.10.003

Lamare, M. (1892). Des mouvements des yeux dans la lecture. *Bulletins et Mémoires de La Société Française d'Ophthalmologie*, *10*, 354-364.

Lan, A., Kalimian, M., Amram, B., & Kofman, O. (2017). Prenatal chlorpyrifos leads to autism-like deficits in C57Bl6/J mice. *Environmental Health: A Global Access Science Source*, *16*(1), 43. https://doi.org/10.1186/s12940-017-0251-3

Land, M. F., & Hayhoe, M. (2001). In what ways do eye movements contribute to everyday activities? *Vision Research*, *41*(25–26), 3559–3565. https://doi.org/10.1016/s0042-6989(01)00102-x

Landa, R. J. (2018). Efficacy of early interventions for infants and young children with, and at risk for, autism spectrum disorders. *International Review of Psychiatry*, *30*(1), 25–39. https://doi.org/10.1080/09540261.2018.1432574

Landry, R., & Bryson, S. E. (2004). Impaired disengagement of attention in young children with autism. *Journal of Child Psychology and Psychiatry*, *45*(6), 1115–1122. https://doi.org/10.1111/j.1469-7610.2004.00304.x

Larsson, M., Weiss, B., Janson, S., Sundell, J., & Bornehag, C.-G. (2009). Associations between indoor environmental factors and parental-reported autistic spectrum disorders in children 6-8 years of age. *Neurotoxicology*, *30*(5), 822–831. https://doi.org/10.1016/j.neuro.2009.01.011

Lazarov, A., Pine, D. S., & Bar-Haim, Y. (2017). Gaze-Contingent Music Reward Therapy for Social Anxiety Disorder: A Randomized Controlled Trial. *American Journal of Psychiatry*, *174*(7), 649–656. https://doi.org/10.1176/appi.ajp.2016.16080894

Libertus, K., Landa, R. J., & Haworth, J. L. (2017). Development of Attention to Faces during the First 3 Years: Influences of Stimulus Type. *Frontiers in Psychology*, *8*. https://www.frontiersin.org/articles/10.3389/fpsyg.2017.01976

Light, J., & McNaughton, D. (2014). From basic to applied research to improve outcomes for individuals who require augmentative and alternative communication: Potential contributions of eye tracking research methods. *Augmentative and Alternative Communication (Baltimore, Md.: 1985)*, *30*(2), 99–105. https://doi.org/10.3109/07434618.2014.906498

Lord, C., Risi, S., DiLavore, P. S., Shulman, C., Thurm, A., & Pickles, A. (2006). Autism from 2 to 9 years of age. *Archives of General Psychiatry*, *63*(6), 694–701. https://doi.org/10.1001/archpsyc.63.6.694

Lord, C., Rutter, M., DiLavore, P. C., Risi, S., Gotham, K., & Bishop, S. L. (2012). *Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2)*. Western Psychological Services.

Lord, C., Rutter, M., & Le Couteur, A. (1994). Autism Diagnostic Interview-Revised: A revised version of a diagnostic interview for caregivers of individuals with possible pervasive developmental disorders. *Journal of Autism and Developmental Disorders*, *24*(5), 659–685.

Lovaas, O. I. (1987). Behavioral treatment and normal educational and intellectual functioning in young autistic children. *Journal of Consulting and Clinical Psychology*, *55*, 3–9. https://doi.org/10.1037//0022-006X.55.1.3

Lovejoy, L. P., Fowler, G. A., & Krauzlis, R. J. (2009). Spatial allocation of attention during smooth pursuit eye movements. *Vision Research*, *49*(10), 1275–1285. https://doi.org/10.1016/j.visres.2009.01.011

Luna, B., Velanova, K., & Geier, C. F. (2008). Development of eye-movement control. *Brain and Cognition*, *68*(3), 293–308. https://doi.org/10.1016/j.bandc.2008.08.019

Ma, D. S., Correll, J., & Wittenbrink, B. (2015). The Chicago face database: A free stimulus set of faces and norming data. *Behavior Research Methods*, *47*(4), 1122–1135. https://doi.org/10.3758/s13428-014-0532-5

Madsen, K. M., Hviid, A., Vestergaard, M., Schendel, D., Wohlfahrt, J., Thorsen, P., Olsen, J., & Melbye, M. (2002). A population-based study of measles, mumps, and rubella vaccination and autism. *The New England Journal of Medicine*, *347*(19), 1477–1482. https://doi.org/10.1056/NEJMoa021134

Maenner, M. J. (2023). Prevalence and Characteristics of Autism Spectrum Disorder Among Children Aged 8 Years—Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2020. *MMWR. Surveillance Summaries*, *72*. https://doi.org/10.15585/mmwr.ss7202a1

Maenner, M. J., Shaw, K. A., Baio, J., EdS1, Washington, A., Patrick, M., DiRienzo, M., Christensen, D. L., Wiggins, L. D., Pettygrove, S., Andrews, J. G., Lopez, M., Hudson, A., Baroud, T., Schwenk, Y., White, T., Rosenberg, C. R., Lee, L.-C., Harrington, R. A., … Dietz, P. M. (2020). Prevalence of Autism Spectrum Disorder Among Children Aged 8 Years—Autism and Developmental Disabilities Monitoring Network, 11 Sites, United States, 2016. *Morbidity and Mortality Weekly Report. Surveillance Summaries (Washington, D.C.: 2002)*, *69*(4), 1–12. https://doi.org/10.15585/mmwr.ss6904a1

Maramara, L. A., He, W., & Ming, X. (2014). Pre- and perinatal risk factors for autism spectrum disorder in a New Jersey cohort. *Journal of Child Neurology*, *29*(12), 1645–1651. https://doi.org/10.1177/0883073813512899

Maresca, G., Pranio, F., Naro, A., De Luca, R., Maggio, M. G., Scarcella, I., De Domenico, C., Bramanti, P., Conti Nibali, V., Portaro, S., & Calabrò, R. S. (2019). Augmentative and alternative communication improves quality of life in the early stages of amyotrophic lateral sclerosis. *Functional Neurology*, *34*(1), 35–43.

Martinez-Marquez, D., Pingali, S., Panuwatwanich, K., Stewart, R. A., & Mohamed, S. (2021). Application of Eye Tracking Technology in Aviation, Maritime, and Construction Industries: A Systematic Review. *Sensors (Basel, Switzerland)*, *21*(13), 4289. https://doi.org/10.3390/s21134289

Mazina, V., Gerdts, J., Trinh, S., Ankenman, K., Ward, T., Dennis, M. Y., Girirajan, S., Eichler, E. E., & Bernier, R. (2015). Interactive effects of copy number variation and maternal infection on autism impairment. *Journal of Developmental and Behavioral Pediatrics : JDBP*, *36*(2), 61–67. https://doi.org/10.1097/DBP.0000000000000126

McCall, R. B., & McGhee, P. E. (1977). The Discrepancy Hypothesis of Attention and Affect in Infants. In I. Č. Užgiris & F. Weizmann (Eds.), *The Structuring of Experience* (pp. 179–210). Springer US. https://doi.org/10.1007/978-1-4615-8786-6_7

McConkie, G. W., Zola, D., Wolverton, G. S., & Burns, D. D. (1978). Eye movement contingent display control in studying reading. *Behavior Research Methods & Instrumentation*, *10*, 154–166. https://doi.org/10.3758/BF03205118

Meisner, O. C., Nair, A., & Chang, S. W. C. (2022). Amygdala connectivity and implications for social cognition and disorders. *Handbook of Clinical Neurology*, *187*, 381–403. https://doi.org/10.1016/B978-0-12-823493-8.00017-1

Meltzoff, A. N., & Moore, M. K. (1977). Imitation of facial and manual gestures by human neonates. *Science (New York, N.Y.)*, *198*(4312), 74–78. https://doi.org/10.1126/science.897687

Miodovnik, A., Engel, S. M., Zhu, C., Ye, X., Soorya, L. V., Silva, M. J., Calafat, A. M., & Wolff, M. S. (2011). Endocrine disruptors and childhood social impairment. *Neurotoxicology*, *32*(2), 261–267. https://doi.org/10.1016/j.neuro.2010.12.009

Mishkin, M., Ungerleider, L. G., & Macko, K. A. (1983). Object vision and spatial vision: Two cortical pathways. *Trends in Neurosciences*, *6*, 414–417. https://doi.org/10.1016/0166-2236(83)90190-X

Modafferi, S., Zhong, X., Kleensang, A., Murata, Y., Fagiani, F., Pamies, D., Hogberg, H. T., Calabrese, V., Lachman, H., Hartung, T., & Smirnova, L. (2021). Gene-Environment Interactions in

Developmental Neurotoxicity: A Case Study of Synergy between Chlorpyrifos and CHD8 Knockout in Human BrainSpheres. *Environmental Health Perspectives*, *129*(7), 77001. https://doi.org/10.1289/EHP8580

Moore, T., Armstrong, K. M., & Fallah, M. (2003). Visuomotor origins of covert spatial attention. *Neuron*, *40*(4), 671–683. https://doi.org/10.1016/s0896-6273(03)00716-5

Moschovakis, A. K. (1996). The superior colliculus and eye movement control. *Current Opinion in Neurobiology*, *6*(6), 811–816. https://doi.org/10.1016/s0959-4388(96)80032-8

Mottron, L., Dawson, M., Soulières, I., Hubert, B., & Burack, J. (2006). Enhanced Perceptual Functioning in Autism: An Update, and Eight Principles of Autistic Perception. *Journal of Autism and Developmental Disorders*, *36*(1), 27–43. https://doi.org/10.1007/s10803-005-0040-7

Muhoza, P., Danovaro-Holliday, M. C., Diallo, M. S., Murphy, P., Sodha, S. V., Requejo, J. H., & Wallace, A. S. (2021). Routine Vaccination Coverage—Worldwide, 2020. *Morbidity and Mortality Weekly Report*, *70*(43), 1495–1500. https://doi.org/10.15585/mmwr.mm7043a1

Mullen, E. M. (1995). *Mullen Scales of Early Learning* (AGS ed.).

Mundy, P., Sullivan, L., & Mastergeorge, A. M. (2009). A parallel and distributed-processing model of joint attention, social cognition and autism. *Autism Research: Official Journal of the International Society for Autism Research*, *2*(1), 2–21. https://doi.org/10.1002/aur.61

Muratori, F., Billeci, L., Calderoni, S., Boncoddo, M., Lattarulo, C., Costanzo, V., Turi, M., Colombi, C., & Narzisi, A. (2019). How Attention to Faces and Objects Changes Over Time in Toddlers with Autism Spectrum Disorders: Preliminary Evidence from An Eye Tracking Study. *Brain Sciences*, *9*(12). https://doi.org/10.3390/brainsci9120344

National Research Council. (2001). *Educating Children with Autism*. https://doi.org/10.17226/10017

Nyström, M., & Holmqvist, K. (2010). An adaptive algorithm for fixation, saccade, and glissade detection in eyetracking data. *Behavior Research Methods*, *42*(1), 188–204. https://doi.org/10.3758/BRM.42.1.188

Ocak, E., Eshraghi, R. S., Danesh, A., Mittal, R., & Eshraghi, A. A. (2018). Central Auditory Processing

Disorders in Individuals with Autism Spectrum Disorders. *Balkan Medical Journal*, *35*(5), 367–372. https://doi.org/10.4274/balkanmedj.2018.0853

Olsen, A. (2012). *The Tobii IVT Fixation Filter Algorithm description*. https://www.semanticscholar.org/paper/The-Tobii-IVT-Fixation-Filter-Algorithm-description-Olsen/66cdac4b380eabb9de3b25c7922c8de92d8d6cae#paper-header

Oulhote, Y., Lanphear, B., Braun, J. M., Webster, G. M., Arbuckle, T. E., Etzel, T., Forget, -Dubois Nadine, Seguin, J. R., Bouchard, M. F., MacFarlane, A., Ouellet, E., Fraser, W., & Muckle, G. (2020). Gestational Exposures to Phthalates and Folic Acid, and Autistic Traits in Canadian Children. *Environmental Health Perspectives*, *128*(2), 027004. https://doi.org/10.1289/EHP5621

Ozonoff, S., Pennington, B. F., & Rogers, S. J. (1991). Executive Function Deficits in High-Functioning Autistic Individuals: Relationship to Theory of Mind. *Journal of Child Psychology and Psychiatry*, *32*(7), 1081–1105. https://doi.org/10.1111/j.1469-7610.1991.tb00351.x

Parish-Morris, J., Chevallier, C., Tonge, N., Letzen, J., Pandey, J., & Schultz, R. T. (2013). Visual attention to dynamic faces and objects is linked to face processing skills: A combined study of children with autism and controls. *Frontiers in Psychology*, *4*. https://doi.org/10.3389/fpsyg.2013.00185

Peiyuan, H., & Kowler, E. (1992). The role of saccades in the perception of texture patterns. *Vision Research*, *32*(11), 2151–2163. https://doi.org/10.1016/0042-6989(92)90076-U

Pellicano, E., & Burr, D. (2012). When the world becomes “too real”: A Bayesian explanation of autistic perception. *Trends in Cognitive Sciences*, *16*(10), 504–510. https://doi.org/10.1016/j.tics.2012.08.009

Pelphrey, K. A., Sasson, N. J., Reznick, J. S., Paul, G., Goldman, B. D., & Piven, J. (2002). Visual Scanning of Faces in Autism. *Journal of Autism and Developmental Disorders*, *32*(4), 249–261. https://doi.org/10.1023/A:1016374617369

Pierce, K., Conant, D., Hazin, R., Stoner, R., & Desmond, J. (2011). Preference for Geometric Patterns Early in Life as a Risk Factor for Autism. *Archives of General Psychiatry*, *68*(1), 101–109.

https://doi.org/10.1001/archgenpsychiatry.2010.113

Pierce, K., Marinero, S., Hazin, R., McKenna, B., Barnes, C. C., & Malige, A. (2016). Eye-tracking Reveals Abnormal Visual Preference for Geometric Images as an Early Biomarker of an ASD Subtype Associated with Increased Symptom Severity. *Biological Psychiatry*, *79*(8), 657–666. https://doi.org/10.1016/j.biopsych.2015.03.032

Pitcher, D., & Ungerleider, L. G. (2021). Evidence for a Third Visual Pathway Specialized for Social Perception. *Trends in Cognitive Sciences*, *25*(2), 100–110. https://doi.org/10.1016/j.tics.2020.11.006

Płużyczka, M. (2018). The First Hundred Years: A History of Eye Tracking as a Research Method. *Applied Linguistics Papers*, *4/2018*, 101–116. https://doi.org/10.32612/uw.25449354.2018.4.pp.101-116

Poletti, B., Carelli, L., Faini, A., Solca, F., Meriggi, P., Lafronza, A., Ciringione, L., Pedroli, E., Ticozzi, N., Ciammola, A., Cipresso, P., Riva, G., & Silani, V. (2018). The Arrows and Colors Cognitive Test (ACCT): A new verbal-motor free cognitive measure for executive functions in ALS. *PLOS ONE*, *13*(8), e0200953. https://doi.org/10.1371/journal.pone.0200953

Poletti, B., Carelli, L., Solca, F., Lafronza, A., Pedroli, E., Faini, A., Zago, S., Ticozzi, N., Ciammola, A., Morelli, C., Meriggi, P., Cipresso, P., Lulé, D., Ludolph, A. C., Riva, G., & Silani, V. (2017). An eye-tracking controlled neuropsychological battery for cognitive assessment in neurological diseases. *Neurological Sciences*, *38*(4), 595–603. https://doi.org/10.1007/s10072-016-2807-3

Pomplun, M., Reingold, E. M., & Shen, J. (2001). Peripheral and parafoveal cueing and masking effects on saccadic selectivity in a gaze-contingent window paradigm. *Vision Research*, *41*(21), 2757–2769. https://doi.org/10.1016/s0042-6989(01)00145-6

Posner, M. (1980). Orienting of Attention. *The Quarterly Journal of Experimental Psychology*, *32*, 3–25. https://doi.org/10.1080/00335558008248231

Prizant, B. M., Wetherby, A. M., Rubin, E., & Laurent, A. C. (2003). The SCERTS Model: A Transactional, Family-Centered Approach to Enhancing Communication and Socioemotional

Abilities of Children With Autism Spectrum Disorder. *Infants & Young Children*, *16*(4), 296.

Qiu, A., Crocetti, D., Adler, M., Mahone, E. M., Denckla, M. B., Miller, M. I., & Mostofsky, S. H. (2009). Basal Ganglia Volume and Shape in Children With Attention Deficit Hyperactivity Disorder. *The American Journal of Psychiatry*, *166*(1), 74–82. https://doi.org/10.1176/appi.ajp.2008.08030426

Ramachandran, V. S., & Oberman, L. M. (2006). Broken mirrors: A theory of autism. *Scientific American*, *295*(5), 62–69. https://doi.org/10.1038/scientificamerican1106-62

Rao, R. P. N., & Ballard, D. H. (1999). Predictive coding in the visual cortex: A functional interpretation of some extra-classical receptive-field effects. *Nature Neuroscience*, *2*(1), Article 1. https://doi.org/10.1038/4580

Rayner, K. (1998). Eye movements in reading and information processing: 20 years of research. *Psychological Bulletin*, *124*(3), 372. https://doi.org/10.1037/0033-2909.124.3.372

Reder, S. M. (1973). On-line monitoring of eye-position signals in contingent and noncontingent paradigms. *Behavior Research Methods & Instrumentation*, *5*(2), 218–228. https://doi.org/10.3758/BF03200168

Reed, P. (2016). *Interventions for Autism: Evidence for Educational and Clinical Practice*. John Wiley & Sons.

Reid, V. M., Dunn, K., Young, R. J., Amu, J., Donovan, T., & Reissland, N. (2017). The Human Fetus Preferentially Engages with Face-like Visual Stimuli. *Current Biology: CB*, *27*(12), 1825-1828.e3. https://doi.org/10.1016/j.cub.2017.05.044

Riby, D., & Hancock, P. J. B. (2009). Looking at movies and cartoons: Eye-tracking evidence from Williams syndrome and autism. *Journal of Intellectual Disability Research: JIDR*, *53*(2), 169–181. https://doi.org/10.1111/j.1365-2788.2008.01142.x

Rilling, J. K. (2014). Comparative primate neuroimaging: Insights into human brain evolution. *Trends in Cognitive Sciences*, *18*(1), 46–55. https://doi.org/10.1016/j.tics.2013.09.013

Riva, D., Taddei, M., & Bulgheroni, S. (2018). The neuropsychology of basal ganglia. *European Journal of Paediatric Neurology: EJPN: Official Journal of the European Paediatric Neurology Society*, *22*(2), 321–326. https://doi.org/10.1016/j.ejpn.2018.01.009

Robain, F., Franchini, M., Kojovic, N., Wood de Wilde, H., & Schaer, M. (2020). Predictors of Treatment Outcome in Preschoolers with Autism Spectrum Disorder: An Observational Study in the Greater Geneva Area, Switzerland. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-020-04430-6

Robain, F., Kojovic, N., Solazzo, S., Glaser, B., Franchini, M., & Schaer, M. (2021). The impact of social complexity on the visual exploration of others' actions in preschoolers with autism spectrum disorder. *BMC Psychology*, *9*(1), 50. https://doi.org/10.1186/s40359-021-00553-2

Rogers, SJ., & Dawson, G. (2010). *Early Start Denver Model for young children with autism: Promoting language, learning, and engagement*. Guilford Press.

Rogers, SJ., Estes, A., Lord, C., Vismara, L., Winter, J., Fitzpatrick, A., Guo, M., & Dawson, G. (2012). Effects of a Brief Early Start Denver Model (ESDM)–Based Parent Intervention on Toddlers at Risk for Autism Spectrum Disorders: A Randomized Controlled Trial. *Journal of the American Academy of Child & Adolescent Psychiatry*, *51*(10), 1052–1065. https://doi.org/10.1016/j.jaac.2012.08.003

Rojas, D. C., Peterson, E., Winterrowd, E., Reite, M. L., Rogers, S. J., & Tregellas, J. R. (2006). Regional gray matter volumetric changes in autism associated with social and repetitive behavior symptoms. *BMC Psychiatry*, *6*, 56. https://doi.org/10.1186/1471-244X-6-56

Rosset, D. B., Rondan, C., Da Fonseca, D., Santos, A., Assouline, B., & Deruelle, C. (2008). Typical emotion processing for cartoon but not for real faces in children with autistic spectrum disorders. *Journal of Autism and Developmental Disorders*, *38*(5), 919–925. https://doi.org/10.1007/s10803-007-0465-2

Rosset, D. B., Santos, A., Da Fonseca, D., Poinso, F., O'Connor, K., & Deruelle, C. (2010). Do children perceive features of real and cartoon faces in the same way? Evidence from typical development and autism. *Journal of Clinical and Experimental Neuropsychology*, *32*(2), 212–218. https://doi.org/10.1080/13803390902971123

Russell, G., Stapley, S., Newlove-Delgado, T., Salmon, A., White, R., Warren, F., Pearson, A., & Ford, T. (2022). Time trends in autism diagnosis over 20 years: A UK population-based cohort study. *Journal of Child Psychology and Psychiatry*, *63*(6), 674–682. https://doi.org/10.1111/jcpp.13505

Sacrey, L.-A. R., Armstrong, V. L., Bryson, S. E., & Zwaigenbaum, L. (2014). Impairments to visual disengagement in autism spectrum disorder: A review of experimental studies from infancy to adulthood. *Neuroscience & Biobehavioral Reviews*, *47*, 559–577. https://doi.org/10.1016/j.neubiorev.2014.10.011

Sacrey, L.-A. R., Bryson, S. E., & Zwaigenbaum, L. (2013). Prospective examination of visual attention during play in infants at high-risk for autism spectrum disorder: A longitudinal study from 6 to 36 months of age. *Behavioural Brain Research*, *256*, 441–450. https://doi.org/10.1016/j.bbr.2013.08.028

Saitovitch, A., Bargiacchi, A., Chabane, N., Brunelle, F., Samson, Y., Boddaert, N., & Zilbovicius, M. (2012). Social cognition and the superior temporal sulcus: Implications in autism. *Revue Neurologique*, *168*(10), 762–770. https://doi.org/10.1016/j.neurol.2012.07.017

Sakurai, T. (2022). Social processes and social environment during development. *Seminars in Cell & Developmental Biology*, *129*, 40–46. https://doi.org/10.1016/j.semcdb.2021.09.016

Salem Yaniv, S., Levy, A., Wiznitzer, A., Holcberg, G., Mazor, M., & Sheiner, E. (2011). A significant linear association exists between advanced maternal age and adverse perinatal outcome. *Archives of Gynecology and Obstetrics*, *283*(4), 755–759. https://doi.org/10.1007/s00404-010-1459-4

Salley, B., & Colombo, J. (2016). Conceptualizing Social Attention in Developmental Research. *Social Development (Oxford, England)*, *25*(4), 687–703. https://doi.org/10.1111/sode.12174

Salvucci, D., & Goldberg, J. (2000). *Identifying fixations and saccades in eye-tracking protocols*. 71–78. https://doi.org/10.1145/355017.355028

Sandoval-Norton, A. H., Shkedy, G., & Shkedy, D. (2019). How much compliance is too much compliance: Is long-term ABA therapy abuse? *Cogent Psychology*, *6*(1), 1641258.

https://doi.org/10.1080/23311908.2019.1641258

Sato, W., Kubota, Y., Kochiyama, T., Uono, S., Yoshimura, S., Sawada, R., Sakihama, M., & Toichi, M. (2014). Increased Putamen Volume in Adults with Autism Spectrum Disorder. *Frontiers in Human Neuroscience*, *8*, 957. https://doi.org/10.3389/fnhum.2014.00957

Schietecatte, I., Roeyers, H., & Warreyn, P. (2012). Can infants' orientation to social stimuli predict later joint attention skills? *The British Journal of Developmental Psychology*, *30*(Pt 2), 267–282. https://doi.org/10.1111/j.2044-835X.2011.02039.x

Schreibman, L., Dawson, G., Stahmer, AC., Landa, R., Rogers, SJ., McGee, GG., Kasari, C., Ingersoll, B., Kaiser, AP., Bruinsma, Y., McNerney, E., Wetherby, A., & Halladay, A. (2015). Naturalistic Developmental Behavioral Interventions: Empirically Validated Treatments for Autism Spectrum Disorder. *Journal of Autism and Developmental Disorders*, *45*(8), 2411–2428. https://doi.org/10.1007/s10803-015-2407-8

Schultz, R. T. (2005). Developmental deficits in social perception in autism: The role of the amygdala and fusiform face area. *International Journal of Developmental Neuroscience*, *23*(2), 125–141. https://doi.org/10.1016/j.ijdevneu.2004.12.012

Schumann, C. M., Barnes, C. C., Lord, C., & Courchesne, E. (2009). Amygdala enlargement in toddlers with autism related to severity of social and communication impairments. *Biological Psychiatry*, *66*(10), 942–949. https://doi.org/10.1016/j.biopsych.2009.07.007

Schumann, C. M., Hamstra, J., Goodlin-Jones, B. L., Lotspeich, L. J., Kwon, H., Buonocore, M. H., Lammers, C. R., Reiss, A. L., & Amaral, D. G. (2004). The Amygdala Is Enlarged in Children But Not Adolescents with Autism; the Hippocampus Is Enlarged at All Ages. *The Journal of Neuroscience*, *24*(28), 6392–6401. https://doi.org/10.1523/JNEUROSCI.1297-04.2004

Semendeferi, K., Lu, A., Schenker, N., & Damasio, H. (2002). Humans and great apes share a large frontal cortex. *Nature Neuroscience*, *5*(3), 272–276. https://doi.org/10.1038/nn814

SFARI. (2023). SFARI Gene Database. *SFARI Gene*. https://gene.sfari.org/database/human-gene/

Shattuck, P. T., Seltzer, M. M., Greenberg, J. S., Orsmond, G. I., Bolt, D., Kring, S., Lounds, J., & Lord,

C. (2007). Change in autism symptoms and maladaptive behaviors in adolescents and adults with an autism spectrum disorder. *Journal of Autism and Developmental Disorders*, *37*(9), 1735–1747. https://doi.org/10.1007/s10803-006-0307-7

Shaw, P., De Rossi, P., Watson, B., Wharton, A., Greenstein, D., Raznahan, A., Sharp, W., Lerch, J. P., & Chakravarty, M. M. (2014). Mapping the development of the basal ganglia in children with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry*, *53*(7), 780-789.e11. https://doi.org/10.1016/j.jaac.2014.05.003

Sherman, J. A. (1971). Imitation and language development. *Advances in Child Development and Behavior*, *6*, 239–272. https://doi.org/10.1016/s0065-2407(08)60084-1

Shic, F., Bradshaw, J., Klin, A., Scassellati, B., & Chawarska, K. (2011). Limited Activity Monitoring in Toddlers with Autism Spectrum Disorder. *Brain Research*, *1380*, 246–254. https://doi.org/10.1016/j.brainres.2010.11.074

Silvers, J. A. (2022). Adolescence as a pivotal period for emotion regulation development. *Current Opinion in Psychology*, *44*, 258–263. https://doi.org/10.1016/j.copsyc.2021.09.023

Simion, F., & Giorgio, E. D. (2015). Face perception and processing in early infancy: Inborn predispositions and developmental changes. *Frontiers in Psychology*, *6*. https://doi.org/10.3389/fpsyg.2015.00969

Sinha, P., Kjelgaard, M. M., Gandhi, T. K., Tsourides, K., Cardinaux, A. L., Pantazis, D., Diamond, S. P., & Held, R. M. (2014). Autism as a disorder of prediction. *Proceedings of the National Academy of Sciences of the United States of America*, *111*(42), 15220–15225. https://doi.org/10.1073/pnas.1416797111

Slater, A., Von der Schulenburg, C., Brown, E., Badenoch, M., Butterworth, G., Parsons, S., & Samuels, C. (1998). Newborn infants prefer attractive faces. *Infant Behavior and Development*, *21*(2), 345–354. https://doi.org/10.1016/S0163-6383(98)90011-X

Slobodin, O., Heffler, K. F., & Davidovitch, M. (2019). Screen Media and Autism Spectrum Disorder: A Systematic Literature Review. *Journal of Developmental & Behavioral Pediatrics*, *40*(4), 303–

311. https://doi.org/10.1097/DBP.0000000000000654

Smith, D. M., & Torregrossa, M. M. (2021). Valence encoding in the amygdala influences motivated behavior. *Behavioural Brain Research*, *411*, 113370. https://doi.org/10.1016/j.bbr.2021.113370

Smith, T. (2001). Discrete Trial Training in the Treatment of Autism. *Focus on Autism and Other Developmental Disabilities*, *16*(2), 86–92. https://doi.org/10.1177/108835760101600204

Spataro, R., Ciriacono, M., Manno, C., & La Bella, V. (2014). The eye-tracking computer device for communication in amyotrophic lateral sclerosis. *Acta Neurologica Scandinavica*, *130*(1), 40–45. https://doi.org/10.1111/ane.12214

Sussman, D., Leung, R. C., Vogan, V. M., Lee, W., Trelle, S., Lin, S., Cassel, D. B., Chakravarty, M. M., Lerch, J. P., Anagnostou, E., & Taylor, M. J. (2015). The autism puzzle: Diffuse but not pervasive neuroanatomical abnormalities in children with ASD. *NeuroImage: Clinical*, *8*, 170–179. https://doi.org/10.1016/j.nicl.2015.04.008

Szatmari, P., Chawarska, K., Dawson, G., Georgiades, S., Landa, R., Lord, C., Messinger, D. S., Thurm, A., & Halladay, A. (2016). Prospective Longitudinal Studies of Infant Siblings of Children With Autism: Lessons Learned and Future Directions. *Journal of the American Academy of Child and Adolescent Psychiatry*, *55*(3), 179–187. https://doi.org/10.1016/j.jaac.2015.12.014

Taylor, B., Miller, E., Farrington, C. P., Petropoulos, M. C., Favot-Mayaud, I., Li, J., & Waight, P. A. (1999). Autism and measles, mumps, and rubella vaccine: No epidemiological evidence for a causal association. *Lancet (London, England)*, *353*(9169), 2026–2029. https://doi.org/10.1016/s0140-6736(99)01239-8

Taylor, L. E., Swerdfeger, A. L., & Eslick, G. D. (2014). Vaccines are not associated with autism: An evidence-based meta-analysis of case-control and cohort studies. *Vaccine*, *32*(29), 3623–3629. https://doi.org/10.1016/j.vaccine.2014.04.085

Thorndike, E. L. (1898). Animal intelligence: An experimental study of the associative processes in animals. *The Psychological Review: Monograph Supplements*, *2*, i–109. https://doi.org/10.1037/h0092987

Thorup, E., Nyström, P., Gredebäck, G., Bölte, S., Falck-Ytter, T., & The EASE Team. (2016). Altered gaze following during live interaction in infants at risk for autism: An eye tracking study. *Molecular Autism*, *7*(1), 12. https://doi.org/10.1186/s13229-016-0069-9

Tick, B., Bolton, P., Happé, F., Rutter, M., & Rijsdijk, F. (2016). Heritability of autism spectrum disorders: A meta-analysis of twin studies. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *57*(5), 585–595. https://doi.org/10.1111/jcpp.12499

Tiede, G., & Walton, K. M. (2019). Meta-analysis of naturalistic developmental behavioral interventions for young children with autism spectrum disorder. *Autism: The International Journal of Research and Practice*, *23*(8), 2080–2095. https://doi.org/10.1177/1362361319836371

Tiura, M., Kim, J., Detmers, D., & Baldi, H. (2017). Predictors of longitudinal ABA treatment outcomes for children with autism: A growth curve analysis. *Research in Developmental Disabilities*, *70*(Supplement C), 185–197. https://doi.org/10.1016/j.ridd.2017.09.008

Todorova, G. K., Pollick, F. E., & Muckli, L. (2021). Special treatment of prediction errors in autism spectrum disorder. *Neuropsychologia*, *163*, 108070. https://doi.org/10.1016/j.neuropsychologia.2021.108070

Toth, K., Munson, J., N. Meltzoff, A., & Dawson, G. (2006). Early Predictors of Communication Development in Young Children with Autism Spectrum Disorder: Joint Attention, Imitation, and Toy Play. *Journal of Autism and Developmental Disorders*, *36*(8), 993–1005. https://doi.org/10.1007/s10803-006-0137-7

Turati, C., Simion, F., Milani, I., & Umiltà, C. (2002). Newborns' preference for faces: What is crucial? *Developmental Psychology*, *38*(6), 875–882. https://doi.org/10.1037/0012-1649.38.6.875

Uno, Y., Uchiyama, T., Kurosawa, M., Aleksic, B., & Ozaki, N. (2012). The combined measles, mumps, and rubella vaccines and the total number of vaccines are not associated with development of autism spectrum disorder: The first case-control study in Asia. *Vaccine*, *30*(28), 4292–4298. https://doi.org/10.1016/j.vaccine.2012.01.093

Unruh, K. E., Sasson, N. J., Shafer, R. L., Whitten, A., Miller, S. J., Turner-Brown, L., & Bodfish, J. W.

(2016). Social Orienting and Attention Is Influenced by the Presence of Competing Nonsocial Information in Adolescents with Autism. *Frontiers in Neuroscience*, *10*, 586. https://doi.org/10.3389/fnins.2016.00586

Van de Cruys, S., Evers, K., Van der Hallen, R., Van Eylen, L., Boets, B., de-Wit, L., & Wagemans, J. (2014). Precise minds in uncertain worlds: Predictive coding in autism. *Psychological Review*, *121*(4), 649–675. https://doi.org/10.1037/a0037665

van der Geest, J. N., Kemner, C., Camfferman, G., Verbaten, M. N., & van Engeland, H. (2002). Looking at images with human figures: Comparison between autistic and normal children. *Journal of Autism and Developmental Disorders*, *32*(2), 69–75. https://doi.org/10.1023/a:1014832420206

van 't Hof, M., Tisseur, C., van Berckelear-Onnes, I., van Nieuwenhuyzen, A., Daniels, A. M., Deen, M., Hoek, H. W., & Ester, W. A. (2021). Age at autism spectrum disorder diagnosis: A systematic review and meta-analysis from 2012 to 2019. *Autism*, *25*(4), 862–873. https://doi.org/10.1177/1362361320971107

Vernetti, A., Senju, A., Charman, T., Johnson, M. H., & Gliga, T. (2018). Simulating interaction: Using gaze-contingent eye-tracking to measure the reward value of social signals in toddlers with and without autism. *Developmental Cognitive Neuroscience*, *29*, 21–29. https://doi.org/10.1016/j.dcn.2017.08.004

Vessoyan, K., Steckle, G., Easton, B., Nichols, M., Mok Siu, V., & McDougall, J. (2018). Using eye-tracking technology for communication in Rett syndrome: Perceptions of impact. *Augmentative and Alternative Communication (Baltimore, Md.: 1985)*, *34*(3), 230–241. https://doi.org/10.1080/07434618.2018.1462848

Vivanti, G., Dissanayake, C., Zierhut, C., Rogers, SJ., & Team, V. A. (2013). Brief Report: Predictors of Outcomes in the Early Start Denver Model Delivered in a Group Setting. *Journal of Autism and Developmental Disorders*, *43*(7), 1717–1724. https://doi.org/10.1007/s10803-012-1705-7

Vivanti, G., Prior, M., Williams, K., & Dissanayake, C. (2014). Predictors of Outcomes in Autism Early

Intervention: Why Don’t We Know More? *Frontiers in Pediatrics*, *2*. https://doi.org/10.3389/fped.2014.00058

Wade, N. J. (2010). Pioneers of eye movement research. *I-Perception*, *1*(2), 33–68. https://doi.org/10.1068/i0389

Wade, N., & Tatler, B. W. (2005). *The Moving Tablet of the Eye: The Origins of Modern Eye Movement Research*. Oxford University Press.

Wang, Q., Hoi, S. P., Wang, Y., Song, C., Li, T., Lam, C. M., Fang, F., & Yi, L. (2019). Out of Mind, Out of Sight? Investigating Abnormal Face Scanning in Autism Spectrum Disorder Using Gaze-Contingent Paradigm. *Developmental Science*, e12856. https://doi.org/10.1111/desc.12856

Wang, Q., Hu, Y., Shi, D., Zhang, Y., Zou, X., Li, S., Fang, F., & Yi, L. (2018). Children with Autism Spectrum Disorder Prefer Looking at Repetitive Movements in a Preferential Looking Paradigm. *Journal of Autism and Developmental Disorders*, *48*(8), 2821–2831. https://doi.org/10.1007/s10803-018-3546-5

Wang, Q., Wall, C. A., Barney, E. C., Bradshaw, J. L., Macari, S. L., Chawarska, K., & Shic, F. (2020). Promoting social attention in 3-year-olds with ASD through gaze-contingent eye tracking. *Autism Research*, *13*(1), 61–73. https://doi.org/10.1002/aur.2199

Warlow, S. M., & Berridge, K. C. (2021). Incentive motivation: “wanting” roles of central amygdala circuitry. *Behavioural Brain Research*, *411*, 113376. https://doi.org/10.1016/j.bbr.2021.113376

Wechsler, D. (2014). *Wechsler intelligence scale for children-fifth edition.* Pearson.

Wegiel, J., Flory, M., Kuchna, I., Nowicki, K., Ma, S. Y., Imaki, H., Wegiel, J., Cohen, I. L., London, E., Wisniewski, T., & Brown, W. T. (2014). Stereological study of the neuronal number and volume of 38 brain subdivisions of subjects diagnosed with autism reveals significant alterations restricted to the striatum, amygdala and cerebellum. *Acta Neuropathologica Communications*, *2*, 141. https://doi.org/10.1186/s40478-014-0141-7

Weiner, K. S., & Gomez, J. (2021). Third Visual Pathway, Anatomy, and Cognition across Species. *Trends in Cognitive Sciences*, *25*(7), 548–549. https://doi.org/10.1016/j.tics.2021.04.002

Weschler, D. (2012). *Weschler Preschool and Primary Scale of Intelligence—Fourth Edition* (Pearson).

WHO. (2022). *Ageing and health*. https://www.who.int/news-room/fact-sheets/detail/ageing-and-health

Woodman, A. C., Smith, L. E., Greenberg, J. S., & Mailick, M. R. (2015). Change in Autism Symptoms and Maladaptive Behaviors in Adolescence and Adulthood: The Role of Positive Family Processes. *Journal of Autism and Developmental Disorders*, *45*(1), 111–126. https://doi.org/10.1007/s10803-014-2199-2

Woodward, N., Finch, C. E., & Morgan, T. E. (2015). Traffic-related air pollution and brain development. *AIMS Environmental Science*, *2*(2), 353–373. https://doi.org/10.3934/environsci.2015.2.353

World Health Organization. (2019). *Guidelines on physical activity, sedentary behaviour and sleep for children under 5 years of age*. World Health Organization. https://apps.who.int/iris/handle/10665/311664

Wu, S., Wu, F., Ding, Y., Hou, J., Bi, J., & Zhang, Z. (2017). Advanced parental age and autism risk in children: A systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, *135*(1), 29–41. https://doi.org/10.1111/acps.12666

Yarbus, A. L. (1967). *Eye Movements and Vision*. Springer US. https://doi.org/10.1007/978-1-4899-5379-7

Young, G. S., Rogers, S. J., Hutman, T., Rozga, A., Sigman, M., & Ozonoff, S. (2011). Imitation from 12 to 24 months in autism and typical development: A longitudinal Rasch analysis. *Developmental Psychology*, *47*(6), 1565–1578. https://doi.org/10.1037/a0025418

Youniss, J., & Haynie, D. L. (1992). Friendship in adolescence. *Journal of Developmental and Behavioral Pediatrics: JDBP*, *13*(1), 59–66.

Zemblys, R., Niehorster, D. C., Komogortsev, O., & Holmqvist, K. (2018). Using machine learning to detect events in eye-tracking data. *Behavior Research Methods*, *50*(1), 160–181. https://doi.org/10.3758/s13428-017-0860-3

Zilbovicius, M., Meresse, I., Chabane, N., Brunelle, F., Samson, Y., & Boddaert, N. (2006). Autism, the superior temporal sulcus and social perception. *Trends in Neurosciences*, *29*(7), 359–366.

https://doi.org/10.1016/j.tins.2006.06.004

Zucker, J. R., Rosen, J. B., Iwamoto, M., Arciuolo, R. J., Langdon-Embry, M., Vora, N. M., Rakeman, J. L., Isaac, B. M., Jean, A., Asfaw, M., Hawkins, S. C., Merrill, T. G., Kennelly, M. O., Maldin Morgenthau, B., Daskalakis, D. C., & Barbot, O. (2020). Consequences of Undervaccination—Measles Outbreak, New York City, 2018-2019. *The New England Journal of Medicine*, *382*(11), 1009–1017. https://doi.org/10.1056/NEJMoa1912514

Zwaigenbaum, L., Bauman, M. L., Choueiri, R., Kasari, C., Carter, A., Granpeesheh, D., Mailloux, Z., Roley, S. S., Wagner, S., Fein, D., Pierce, K., Buie, T., Davis, P. A., Newschaffer, C., Robins, D., Wetherby, A., Stone, W. L., Yirmiya, N., Estes, A., … Natowicz, M. R. (2015). Early Intervention for Children With Autism Spectrum Disorder Under 3 Years of Age: Recommendations for Practice and Research. *Pediatrics*, *136*(Supplement 1), S60–S81. https://doi.org/10.1542/peds.2014-3667E

Zwaigenbaum, L., Bryson, S., Rogers, T., Roberts, W., Brian, J., & Szatmari, P. (2005). Behavioral manifestations of autism in the first year of life. *International Journal of Developmental Neuroscience*, *23*(2–3), 143–152. https://doi.org/10.1016/j.ijdevneu.2004.05.001

# 6 – Annex

## 6.1 Full length article: Study 1

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ORIGINAL PAPER

# Predictors of Treatment Outcome in Preschoolers with Autism Spectrum Disorder: An Observational Study in the Greater Geneva Area, Switzerland

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**Abstract**
This study aims to identify predictors of treatment outcome in young children with ASD within a European context, where service provision of intervention remains sporadic. We investigated whether a child's age at baseline, intensity of the intervention provided, type of intervention, child's level of social orienting and cognitive skills at baseline predicted changes in autistic symptoms and cognitive development after 1 year of intervention, in a sample of 60 children with ASD. Our results strongly support early and intensive intervention. We also observed that lower cognitive skills at baseline were related to greater cognitive gains. Finally, we show that a child's interest in social stimuli may contribute to intervention outcome.

**Keywords** Predictors · Early intervention · Intensity of intervention · Social orienting · Early Start Denver Model · Community treatment

## Introduction

Autism spectrum disorder (ASD) is a group of pervasive neurodevelopmental disorders characterized by impairments in communication, social interactions and the presence of restricted and repetitive behaviors (DSM-5; American Psychiatric Association 2013). The main aim of an effective therapeutic intervention for individuals with ASD is to reduce symptom severity, while increasing cognitive functioning and adaptive skills. Over the past decade, naturalistic developmental behavioral interventions (NDBI), which emphasize a child's early development of social communication by using developmentally appropriate behavioral techniques in a natural environment, have been at the forefront of research based on their positive outcomes (Dawson et al. 2010; Kasari et al. 2006; Koegel et al. 1999; Prizant et al. 2006; Schreibman et al. 2015). However, as the symptoms of ASD are heterogeneous, more research is needed to better understand the mechanisms of successful interventions and to identify which variables predict optimal outcomes. As emphasized by Vivanti et al. (2014), studying which variables predict what outcome is essential to being able to individualize early intervention programs based on a child's clinical and developmental profile.

## Age at Intervention Start

Throughout the literature, there is a consensus that a child's age at the start of intervention is one of the most decisive variables influencing outcome (Dawson 2008; Flanagan et al. 2012; French and Kennedy 2017; Green et al. 2017; Sullivan et al. 2014; Harris and Handleman 2000; Klintwall et al. 2015; Reichow 2012; Fenske et al. 1985). Most authors speculate that the effectiveness of early intervention in young children with ASD relies on the high cerebral plasticity at this age (Dawson 2008; Ventola et al. 2013). The current recommendation is thus to intervene as early

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as possible, ideally before 3-years-of-age (Kasari et al. 2012; Landa et al. 2013; National Research Council 2001; Zwaigenbaum et al. 2015), and if possible before autistic symptoms are fully developed (Green et al. 2017; Rogers et al. 2014).

## Intensity of Intervention

In addition to the age at which a child receives intervention, current guidelines also advocate that the number of intervention hours received per week, or "intensity", is also important for outcome (Eldevik et al. 2009; Granpeesheh et al. 2009; Linstead et al. 2017a, b; Lovaas et al. 1974), explaining up to 60% of the outcome variance (Linstead et al. 2017a). However, studies do not always report benefits of a higher number of hours of intervention when compared to less intensive therapeutic interventions. For example, among a sample of children receiving a variety of intervention approaches, Darrou et al. (2010) did not identify any significant correlation between the amount of hours of intervention and outcome. Similarly, Fernell et al. (2011) did not observe a better outcome in children receiving high intensity of ABA intervention compared to a group receiving lower intensity of ABA-based intervention. Finally, in a meta-analysis, Maw and Haga (2018) suggested that the benefits from more hours of intervention varied from one type of intervention to another, so that the type of intervention should be taken into account when assessing the effect of intensity of the intervention on the outcome. Taken together, these discrepancies among studies suggest that more research is needed to establish a clear relationship between the number of hours of intervention and outcomes.

## Cognitive Skills

Another predictor frequently reported as influencing intervention outcome is the child's level of cognitive functioning at the onset of intervention. Considering that up to 30% of children with ASD have associated intellectual disability (Polyak et al. 2015), and that maladaptive behaviors associated with ASD are also related to lower cognitive functioning (Shattuck et al. 2007; Woodman et al. 2015), this relationship between cognitive skills and outcome appears highly relevant. Numerous studies advocate that children with higher cognitive skills are more likely to show better outcome in terms of gain in verbal skills (Anderson et al. 2007), adaptive skills (Fernell et al. 2011; Tiura et al. 2017), higher attendance rate to regular school (Harris and Handleman 2000), and higher gain in communication or socio-emotional skills (Tiura et al. 2017) compared to children with lower cognitive skills at baseline. However, the relationship between cognitive functioning at baseline and outcome might be more nuanced. In a meta-analysis, Reed (2016) suggested an inverse U-shape relationship between IQ levels at baseline and subsequent outcome, whereby studies including children with an average baseline IQ between 50 and 60 showed the most important cognitive or functional gain, while studies comprising children with a mean IQ lower than 40 or higher than 75 reported more modest gains. Taken together, these results suggest a complex relationship between IQ and outcome.

## Social Orienting

A characteristic that has been less studied as a potential predictor of outcome, but that is generally acknowledged as a robust biomarker for ASD, is social orienting (Jones et al. 2014; Jones and Klin 2013; Morrisey et al. 2018; Pierce et al. 2011, 2016). Social orienting or social attention, represents the extent to which the child attends to social information and is generally measured using eye-tracking tools. Pierce et al. (2011, 2016) developed a 1-min visual preference task displaying social versus geometric stimuli, which demonstrated an ability to distinguish between two different patterns of visual exploration among children with ASD: on the one hand, the geometric responders (GR) that spent more time looking at the geometric stimuli, and on the other hand, the social responders (SR) that were more interested in the social stimuli. The authors observed that the GR group exhibited more autism symptoms and weaker cognitive abilities, when compared to the SR group (Pierce et al. 2016). Using a similar paradigm, it was recently reported that SR young children showed a more significant decrease of autistic symptoms over time than GR children (Franchini et al. 2016, 2018), suggesting that social orienting at baseline could represent a promising predictor of outcome. However, another study measuring social orienting using a different eye-tracking paradigm (Vivanti et al. 2013) did not observe any significant relationship between social orienting and outcome after a year in a group of children who received Early Start Denver Model (ESDM) intervention. Given its important role during early development, especially in the development of socio-communicative skills (Franchini et al. 2019; Schietecatte et al. 2011), more research is needed to establish a clear relationship between social orienting levels at baseline and its impact on intervention outcome.

## European Context

Until relatively recently, most studies on autism intervention have been conducted in the United States, and predictors of intervention outcome have scarcely been studied in a European context. A recent survey highlighted great disparity among service provision of early intervention across European countries for children under the age of 7 (Salomone et al. 2016). While 64% of the children with ASD received speech therapy, 55% received behavioral intervention and up to 10% of the children did not receive any intervention. They showed that the type of intervention received was influenced by the educational level of the parents, verbal skills of the child, time passed since the child's diagnosis and the European region where the family resides. While the majority of European studies have focused on the importance of early diagnosis, the implementation of Early and Intensive Behavioral Intervention (EIBI) programs, and their feasibility and results (Colombi et al. 2016; Fernell et al. 2011; Freitag et al. 2012; Remington et al. 2007; Salt et al. 2001; Touzet et al. 2017); only a small number of studies have explored the factors that predict intervention outcome in a European context (Benvenuto et al. 2016; Bieleninik et al. 2017; Narzisi et al. 2015).

This lack of knowledge regarding the efficacy of interventions provided in Europe and their related predictors of outcome encouraged us to conduct the present study. We chose to use an observational approach, as promoted by Benvenuto et al. (2016), Rosenbaum (2010) or Worrall (2007), which allowed us to obtain a more realistic representation of the possible treatment outcome predictors in the French-speaking region around Geneva, Switzerland. We used a group of 60 preschoolers diagnosed with ASD to examine putative outcome predictors described in the literature, such as intensity of intervention, age, cognitive level, and social orienting at baseline. We then explored the relationship between these variables and intervention outcome after 1 year of treatment, measured by the improvement of autism symptom severity and cognitive functioning. We hypothesized that children who were younger, more socially oriented and/or had a higher level of cognitive functioning at intake and who received a more intensive intervention would show a greater decrease in their autism symptoms and better cognitive gains over the first year of treatment.

## Method

### Participants

The study included a sample of 60 preschoolers with ASD (all males), who were aged 1.6-to-5-years-old at their first assessment (mean = 3.0 ± 0.8 SD) (see Table 1). All children received a clinical diagnosis of ASD according to the DSM-5 (American Psychiatric Association 2013) before their inclusion in the study. We further confirmed the diagnosis using the Autism Diagnostic Observation Schedule-G, or 2nd edition (ADOS; Lord et al. 2000, 2012). The ADOS-2 evaluation consists of a semi-structured assessment of restricted and repetitive behaviors (RRB), communication, and reciprocal social interactions (social affect, SA). Children with known Fragile X, Rett, Phelan-McDermid syndromes or neurofibromatosis, or with major somatic disorders, were excluded. All children received approximately 1 year of early intervention (mean time interval = 12.1 months ± 0.1 SD), at different intensities and with different treatment approaches. In our sample, 22 children received an early and intensive intervention, based on the ESDM intervention (Rogers and Dawson 2010), while the remaining 38 children received treatments available in their community (community treatment, CT). It is important to note that in both groups, most of the children received multiple interventions (70% of the total sample). Furthermore, as this study focused on the possible impact of different variables on intervention outcome, we did not include typically developing children as a control group. Lastly, all participants' parents provided their written consent before the start of the evaluation, in accordance with protocols approved by the institutional review board of the institution where the research was carried out.

### Procedure and Measures

First, an initial encounter with each child's parents was scheduled to explain the research protocol. Parents were given a questionnaire to collect information regarding intervention frequency and specifications, along with written consent to take part in the study, before starting the evaluations. To assess the symptom severity of RRB, SA and overall ASD symptom levels, we used the ADOS calibrated severity score algorithms (Gotham et al. 2009; Hus et al. 2014). The ADOS calibrated severity scores are divided by "RRB" severity score, "SA" severity score and "Total" severity score. While RRB and SA severity scores represent distinct symptom measures, the "Total" severity score represents a combination of the RRB and SA severity scores in order to estimate an overall symptomatology level. Using these calibrated scores allowed us to compare children with various developmental and language levels (across modules and editions of the ADOS). All ADOS were administered by a trained examiner, videotaped and later rated in team with at least one examiner who had established research reliability on the ADOS-2. Research reliability was assessed, following common procedures, by reaching an 80% cut-off of similar ratings with a certified trainer. Research reliable clinicians were not blind to the intervention received, but did not take part in the intervention itself. Additionally, the Psychoeducational Profile—Third Edition (PEP-3; Schopler et al. 2005) was administered to evaluate the developmental profile of the child. The PEP-3 provides a measure of cognitive verbal and preverbal skills that we then converted into a developmental quotient (DQ) by dividing the developmental level by the chronological age, as already used in many studies (e.g., Franchini et al. 2018; Kawabe et al. 2016).
Finally, we used a visual preference eye-tracking task (biological vs. geometric motion) to estimate each child's

Table 1 Sample demographics

| Intervention group | Social Orienting group | Age at baseline | Hours of intervention | Restricted and repetitive behaviors | | Social affect | | Total | | Developmental quotient | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | T1 | T2 | T1 | T2 | T1 | T2 | T1 | T2 |
| Community treatment ($n$ = 38) | Geometric responders ($n$ = 23) | 3.36 ± 0.72 | 4.78 ± 5.97 | 8.96 ± 1.22 | 9.43 ± 1.04 | 6.39 ± 2.11 | 6.26 ± 1.74 | 7.52 ± 1.65 | 7.57 ± 1.56 | 63.97 ± 20.66 | 71.26 ± 25.41 |
| | Social responders ($n$ = 15) | 3.20 ± 1.10 | 5.77 ± 7.57 | 8.40 ± 1.81 | 8.13 ± 2.45 | 5.67 ± 1.84 | 5.60 ± 2.53 | 6.53 ± 2.10 | 6.60 ± 2.47 | 80.06 ± 30.52 | 87.71 ± 26.91 |
| Total CT ($n$ = 38) | | 3.30 ± 0.88 | 5.17 ± 6.57 | 8.74 ± 1.48 | 8.92 ± 1.82 | 6.11 ± 2.01 | 6.00 ± 2.08 | 7.13 ± 1.88 | 7.18 ± 2.00 | 70.32 ± 25.88 | 77.76 ± 26.91 |
| ESDM-based intervention ($n$ = 22) | Geometric responders ($n$ = 9) | 2.52 ± 0.35 | 20.28 ± 0.83 | 8.56 ± 2.19 | 9.22 ± 1.09 | 7.44 ± 1.68 | 6.22 ± 1.10 | 8.11 ± 1.76 | 7.22 ± 1.79 | 65.81 ± 21.92 | 80.56 ± 25.54 |
| | Social responders ($n$ = 13) | 2.61 ± 0.39 | 19.23 ± 1.83 | 8.25 ± 1.96 | 9.00 ± 1.60 | 7.54 ± 1.94 | 5.15 ± 1.77 | 8.15 ± 2.04 | 6.38 ± 2.02 | 77.82 ± 21.98 | 89.77 ± 17.75 |
| Total ESDM ($n$ = 22) | | 2.57 ± 0.37 | 19.66 ± 1.57 | 8.38 ± 2.01 | 9.10 ± 1.38 | 7.50 ± 1.79 | 5.59 ± 1.59 | 8.14 ± 1.89 | 6.73 ± 1.93 | 72.91 ± 22.26 | 86.00 ± 21.21 |
| | Total geometric responders ($n$ = 32) | 3.13 ± 0.74 | 9.14 ± 8.70 | 8.84 ± 1.53 | 9.38 ± 1.04 | 6.69 ± 2.02 | 6.25 ± 1.57 | 7.69 ± 1.67 | 7.47 ± 1.61 | 64.49 ± 20.68 | 73.88 ± 25.39 |
| | Total social responders ($n$ = 28) | 2.93 ± 0.89 | 12.02 ± 8.83 | 8.33 ± 1.84 | 8.52 ± 2.12 | 6.54 ± 2.08 | 5.39 ± 2.18 | 7.29 ± 2.19 | 6.50 ± 2.24 | 79.02 ± 26.44 | 88.67 ± 22.73 |
| Total (N = 60) | | 3.03 ± 0.81 | 10.48 ± 8.81 | 8.61 ± 1.68 | 8.98 ± 1.67 | 6.62 ± 2.03 | 5.85 ± 1.91 | 7.50 ± 1.93 | 7.02 ± 1.97 | 71.27 ± 24.46 | 80.78 ± 25.11 |

Values in the table represent Mean ± Standard Deviation

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level of social orienting (Franchini et al. 2016, 2017, 2018), inspired by the task designed by Pierce et al. (2011). We applied the same metrics as those described in previous studies conducted by Franchini et al. (2016, 2017, 2018). The task consisted of a one minute, split screen simultaneous presentation of dynamic geometric motion, (similar to that of screensavers) on one side, and dynamic biological motion in the form of videos of children moving around on the other half of the screen. The task was administered using Tobii Studio software 3.1.6 on a TX300 Tobii eye-tracker system. Children were sat either alone on a chair or on their parent's lap, at an approximate distance of 60 cm from the screen. After completing a five-point calibration adapted to toddlers, children looked freely at the screen without any prior specific indication. We drew areas of interest on the videos to delimit biological and geometrical motion to identify the participant's preference. We then derived a percentage of social orienting from the time spent fixating biological motion (using Tobii software 3.1.6), the total time spent looking at the screen was divided by the time spent looking at biological motion. As already done in several studies (Franchini et al. 2016, 2017, 2018; Pierce et al. 2011, 2016), we split children into two groups, where participants looking at the biological stimuli for more than 50% of the total viewing time were categorized as Social Responders (SR), and children looking mostly at the geometric stimuli were considered to be Geometric Responders (GR). To avoid any bias, participants who looked at the screen during less than 50% of the task were removed from our sample. Participants repeated this protocol approximately 1 year later to measure changes following intervention. For the outcome measures, we calculated a raw change over time for each measure [e.g. (ADOS SA score at Time 2—ADOS SA score at Time 1)]. Ultimately, our design included the following five possible predictors of outcome: (1) age at baseline: age at the first visit; (2) intensity of intervention: number of hours per week of intervention the child received during the year; (3) intervention group: dichotomous variable of the intervention received (ESDM or CT); (4) social orienting group: dichotomous variable of social orienting at baseline (SR or GR); and (5) developmental quotient at baseline: cognitive functioning at baseline assessed by PEP-3, CVP subdomain, as described above.

We evaluated these variables to measure their relation to four outcome measures: (1) ADOS RRB change: restricted interest and repetitive behaviors change over the year; (2) ADOS SA change: social communication skills change over the year; (3) ADOS Total change: overall symptom level change over the year; and (4) DQ change: cognitive functioning change over the year.

### Analysis Strategy

We performed a repeated measures ANCOVA in order to identify changes over time as a main effect, as well as potential interactions between groups of intervention and social orienting groups on the outcome. To do so, we used severity scores at baseline and severity scores 1 year later as dependent variables; intervention group (ESDM vs. CT) and social orienting group (SR vs. GR) as between-subject factors. In addition, we controlled for age at baseline as well as intensity of intervention and developmental quotient at baseline using mean values (see Table 1). Model resulted in a 2 (time) × 2 (intervention group) × 2 (social orienting group) repeated measures ANCOVA where age at baseline, intensity of intervention and developmental quotient were included as covariates. In addition, pairwise comparisons corrected for Bonferroni were used to determine between and within group differences. These analyses were performed using IBM SPSS Statistics for MacIntosh, Version 24.0 (Armonk, NY: IBM Corp.), and graphs were plotted using GraphPad Prism 7.0a (GraphPad Software, La Jolla California USA, www.graphpad.com) version for Macintosh. All data underwent an outlier identification test using GraphPad Prism 7.0a (ROUT, 1%), a method combining regression and outlier removal (1% corresponding to the false discovery rate; Motulsky and Brown 2006). We performed additional stepwise regression when there was more than one significant variable influencing the outcome in order to establish a hierarchy between significant predictors. Finally, we performed post-hoc analyses to examine whether or not the inversed U-shaped relationship between IQ and outcome suggested by Reed (2016) could be related to a relationship between DQ scores and the presence of maladaptive behaviors as we believe that it could impact the test-taking ability of children. To do so, we used the PEP-3 "Maladaptive behavior" composite score which evaluates inappropriate social interactions, idiosyncratic language, and restricted and repetitive behaviors. All items are very specific to maladaptive behaviors occurring in ASD and aim to orient diagnosis. We used standard scores to assess maladaptive behaviors level at baseline where lower scores imply more maladaptive behaviors. We used regressions to explore if the Maladaptive scores at baseline were predictive of the DQ scores at baseline, at T2 and of the over time change. Finally, we used regression to see if the changes in Maladaptive scores were predictive of the DQ changes over time.

Table 2 Repeated measures ANCOVA including mean age at baseline, intensity of intervention and DQ at baseline as covariates

| Measure | Source | *df* | MS | F | *p* | %p² |
|---|---|---|---|---|---|---|
| Restricted and repetitive behavior severity | Time | 1 | 0.127 | 0.100 | 0.753 | 0.002 |
| | Time × Intensity of intervention | 1 | 0.838 | 0.661 | 0.420 | 0.013 |
| | Time × Age at baseline | 1 | 1.576 | 1.244 | 0.270 | 0.023 |
| | Time × DQ at baseline | 1 | 0.923 | 0.728 | 0.397 | 0.014 |
| | Time × Group of intervention | 1 | 0.015 | 0.011 | 0.915 | 0.000 |
| | Time × Social orienting group | 1 | 1.185 | 0.935 | 0.338 | 0.018 |
| | Time × Group of intervention x Social orienting group | 1 | 1.695 | 1.338 | 0.253 | 0.025 |
| | Error | 53 | 1.267 | | | |
| Social affect severity | Time | 1 | 3.431 | 1.591 | 0.213 | 0.029 |
| | Time × Intensity of intervention | 1 | 1.704 | 0.790 | 0.378 | 0.015 |
| | Time × Age at baseline | 1 | 0.871 | 0.404 | 0.528 | 0.008 |
| | Time × DQ at baseline | 1 | 0.120 | 0.056 | 0.814 | 0.001 |
| | Time × Group of intervention | 1 | 10.934 | 5.072 | 0.029* | 0.087 |
| | Time × Social orienting group | 1 | 1.555 | 0.721 | 0.400 | 0.013 |
| | Time × Group of intervention x Social orienting group | 1 | 0.2391 | 1.109 | 0.297 | 0.020 |
| | Error | 53 | 2.157 | | | |
| Total severity | Time | 1 | 5.530 | 2.933 | 0.093 | 0.052 |
| | Time × Intensity of intervention | 1 | 1.573 | 0.834 | 0.365 | 0.015 |
| | Time × Age at baseline | 1 | 1.614 | 0.856 | 0.359 | 0.016 |
| | Time × DQ at baseline | 1 | 0.574 | 0.304 | 0.583 | 0.006 |
| | Time × Group of intervention | 1 | 7.229 | 3.834 | 0.056 | 0.067 |
| | Time × Social orienting group | 1 | 1.552 | 0.823 | 0.368 | 0.015 |
| | Time × Group of intervention x Social orienting group | 1 | 1.251 | 0.663 | 0.419 | 0.012 |
| | Error | 53 | 1.886 | | | |
| Developmental quotient scores | Time | 1 | 3914.499 | 20.927 | 0.000* | 0.283 |
| | Time × Intensity of intervention | 1 | 114.136 | 0.610 | 0.438 | 0.011 |
| | Time × Age at baseline | 1 | 912.931 | 4.881 | 0.032* | 0.084 |
| | Time × DQ at baseline | 1 | 2883.359 | 15.415 | 0.000* | 0.225 |
| | Time × Group of intervention | 1 | 72.489 | 0.388 | 0.536 | 0.007 |
| | Time × Social orienting group | 1 | 124.628 | 0.666 | 0.418 | 0.012 |
| | Time × Group of intervention x Social orienting group | 1 | 22.746 | 0.122 | 0.729 | 0.002 |
| | Error | 53 | 187.054 | | | |

Covariates appearing in the model are evaluated at the mean value for Age at baseline, Intensity of intervention, and DQ at baseline

*$p < .05$

## Results

### RRB Change

A repeated measures ANCOVA, with a Greenhouse–Geisser correction including age at baseline, intensity of intervention and DQ at baseline as covariates, showed that RRB severity scores did not significantly differ between T1 and T2 ($p > 0.05$; see Table 2; Fig. 1a). In the overall sample, child RRB severity scores stayed stable after 1 year of intervention. Moreover, between subject factors such as intervention group or social orienting group did not impact RRB severity scores at baseline and 1 year later. In other words, children belonging to CT or ESDM intervention group (see Fig. 1b), or being qualified as SR or GR had similar mean RRB severity scores at T1 and T2 (see Fig. 1c).

Age at baseline, intensity of intervention and DQ at baseline were not predictive of the RRB mean change over time (all $p > 0.05$; see Table 2). Interaction between subject factors and time did not appear significant, meaning that the changes observed in mean RRB severity scores from T1 to T2 were statistically equivalent in both intervention groups ($p > 0.05$; see Table 2); as well as the changes observed in both social orienting groups ($p > 0.05$; see Table 2).

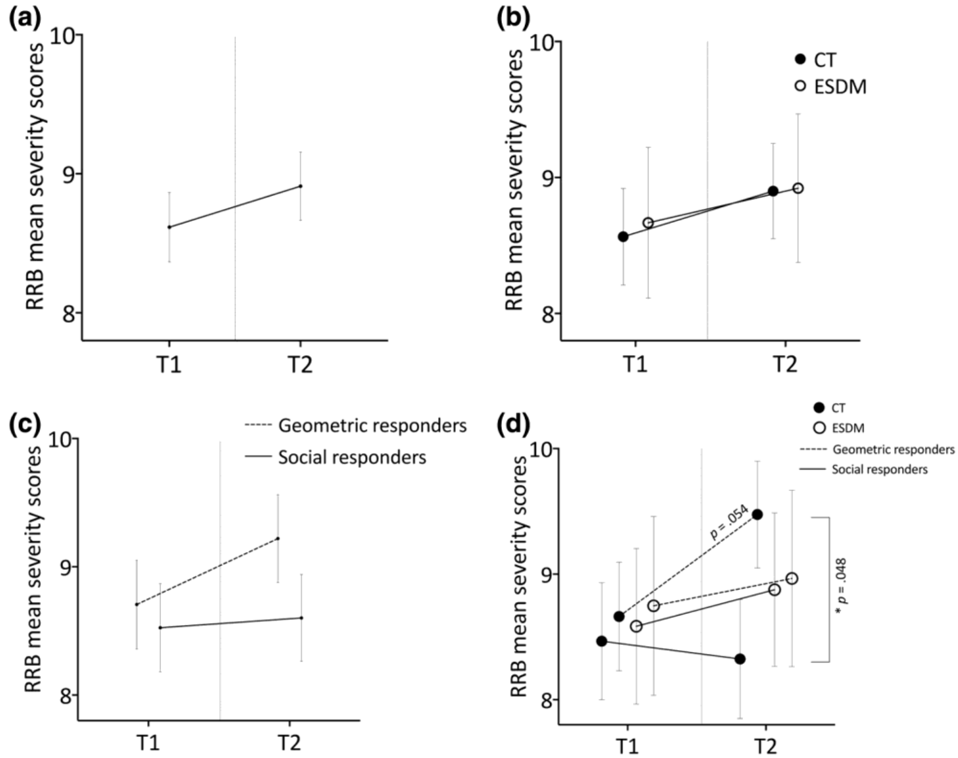


Fig. 1 Restricted and Repetitive Behavior symptom severity changes over time, **a** RRB overall mean severity scores at baseline and after 1 year of intervention, **b** RRB mean severity scores at baseline and after 1 year of intervention by Intervention group (ESDM vs. CT) **c** RRB mean severity scores at baseline and after 1 year of intervention by Social orienting group (Social responders vs. Geometric responders) **d** RRB mean severity scores at baseline and after 1 year of intervention in ESDMxGeo, ESDMxSoc, CTxGeo and CTxSoc. Framed values represent results from the ANCOVA, values in the graphs represent pairwise comparisons

Finally, there was no interaction between time, intervention group and social orienting group ($p > 0.05$; see Table 2), reflecting the fact that the overall mean RRB change did not differ according to the combination of between factors (intervention group and social orienting group) over time. However, post hoc tests using the Bonferroni correction revealed that children receiving CT and categorized as GR at baseline tend to increase their mean

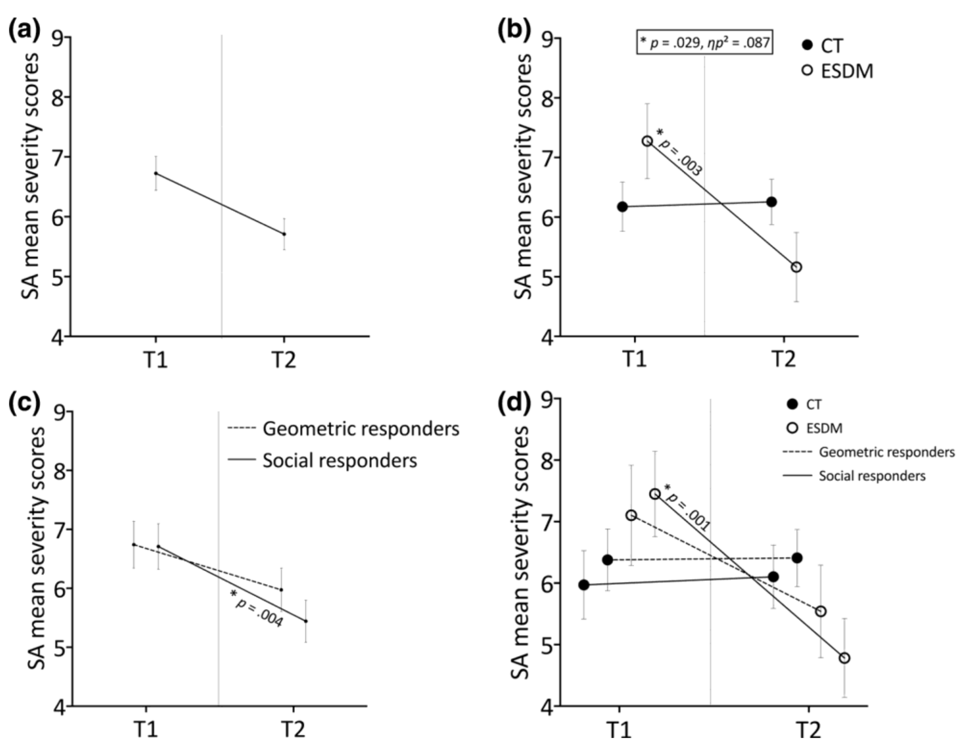


Fig. 2 Social Affect symptom severity changes over time, **a** SA overall mean severity scores at baseline and after 1 year of intervention, **b** SA mean severity scores at baseline and after 1 year of intervention by Intervention group (ESDM vs. CT) **c** SA mean severity scores at baseline and after 1 year of intervention by Social orienting group (Social responders vs. Geometric responders) **d** SA mean severity scores at baseline and after 1 year of intervention in ESDMxGeo, ESDMxSoc, CTxGeo and CTxSoc. Framed values represent results from the ANCOVA, values in the graphs represent pairwise comparisons

RRB severity scores after 1 year of intervention by an average of 0.811 ($p = 0.054$; see Fig. 1d) which resulted in a significant 1.150 ($p = 0.048$) average difference at T2 between means of children receiving CT and being SR and CT children categorized as GR (see Fig. 1d).

## SA Change

A repeated measures ANCOVA with a Greenhouse–Geisser correction controlling for age at baseline, intensity of intervention and DQ at baseline showed that mean SA severity scores did not differed significantly between T1 and T2 ($p > 0.05$; see Table 2; Fig. 2a). Age at baseline, intensity of intervention and DQ at baseline were not predictive of the SA mean change over time (all $p > 0.05$; see Table 2).

However, we identified a significant interaction between time and the intervention group ($F(1,53) = 5.072$, $p = 0.029$; see Table 2; Fig. 2b), suggesting that the intervention received had an impact on the changes observed in SA severity scores over time. Post-hoc tests corrected using Bonferroni indicated no significant differences between intervention groups mean SA severity scores at T1 and T2, but a significant change over time was observed in children receiving ESDM based intervention with an average decrease of − 2.114 ($p = 0.003$, see Fig. 2b). There was no significant interaction between time and social orienting group ($p > 0.05$; see Table 2; Fig. 2c). SA mean severity scores were equivalent at baseline between SR and GR and did not differ after 1 year of intervention despite a significant average decrease of − 1.266 ($p = 0.004$; see Fig. 2c) over time in the SR group.

Finally, there was no significant interaction between time, intervention group and social orienting group ($p > 0.05$; see Table 2; Fig. 2d). Post-hoc tests, using Bonferroni correction indicated no differences at T1 and T2 between all combination of between factors (see Fig. 2d). However, it indicated that the mean SA severity scores of children receiving ESDM based intervention and belonging to the SR group significantly decreased their SA scores on the ADOS by − 2.665 ($p = 0.001$; see Fig. 2d) after 1 year of intervention.

## Total Change

A repeated measures ANCOVA with a Greenhouse–Geisser correction controlling for age at baseline, intensity of intervention and DQ at baseline showed no significant difference between T1 and T2 regarding mean Total severity scores ($p > 0.05$; see Table 2; Fig. 3a).

Age at baseline, intensity of intervention and DQ at baseline were not predictive of the mean Total change over time (all $p > 0.05$; see Table 2). However, we identified a trend between time and the intervention group ($F(1,53) = 3.834$, $p = 0.056$; see Table 2; Fig. 3b), implying that the type of intervention received slightly impacted the mean change observed in Total severity scores over time. Post-hoc tests corrected using Bonferroni indicated that there were no

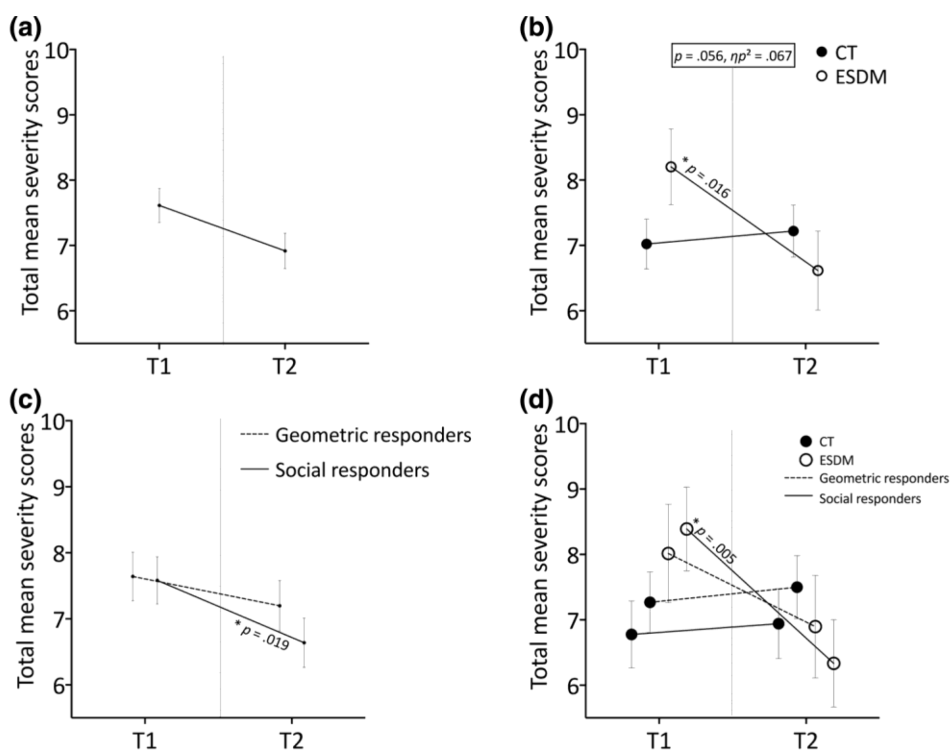


Fig. 3 Total symptom severity changes over time, **a** Total overall mean severity scores at baseline and after 1 year of intervention, **b** Total mean severity scores at baseline and after 1 year of intervention by Intervention group (ESDM vs. CT) **c** Total mean severity scores at baseline and after 1 year of intervention by Social orienting group (Social responders vs. Geometric responders) **d** Total mean severity scores at baseline and after 1 year of intervention in ESDMxGeo, ESDMxSoc, CTxGeo and CTxSoc. Framed values represent results from the ANCOVA, values in the graphs represent pairwise comparisons

differences between groups of intervention at T1 and T2, but children receiving ESDM based intervention significantly decreased their mean SA severity scores over time experiencing an average decrease of − 1.587 ($p = 0.016$; see Fig. 3b). Regarding the social orienting groups, there was no interaction with time ($p > 0.05$; see Table 2; Fig. 3c). Despite the absence of interaction and no significant differences at T1 and T2 between SR and GR, post-hoc tests using the Bonferroni correction revealed that SR children exhibited a significant − 0.945 ($p = 0.019$; see Fig. 3c) decrease of their Total severity scores over time.

Finally, there was no significant interaction effect between time, intervention group and social orienting group on the mean Total severity scores ($p > 0.05$; see Table 2; Fig. 3d). Pairwise comparisons did not identify any differences between groups at T1 and T2 (all $p > 0.05$). However, SR children who received ESDM based intervention experienced a significant decrease over time of − 2.055 ($p = 0.005$; see Fig. 3d) regarding their mean Total severity scores.

## DQ Change

A repeated measures ANCOVA with a Greenhouse–Geisser correction controlling for age at baseline, intensity of intervention and DQ at baseline indicated a significant 10.410 increase of DQ mean scores over time ($F(1,53) = 20.927$, $p < 0.001$; see Table 2, Fig. 4a). Children included in the study improved their DQ by an average of 10.4 points during their first year of intervention.

Age at baseline appeared to significantly predict DQ change over time ($F(1,53) = 4.881$, $p = 0.032$; see Table 2; Fig. 5a). DQ at baseline also predicted DQ change over time ($F(1,53) = 15.415$, $p < 0.001$; see Table 2; Fig. 5b). Intensity of intervention did not impact the DQ change over time

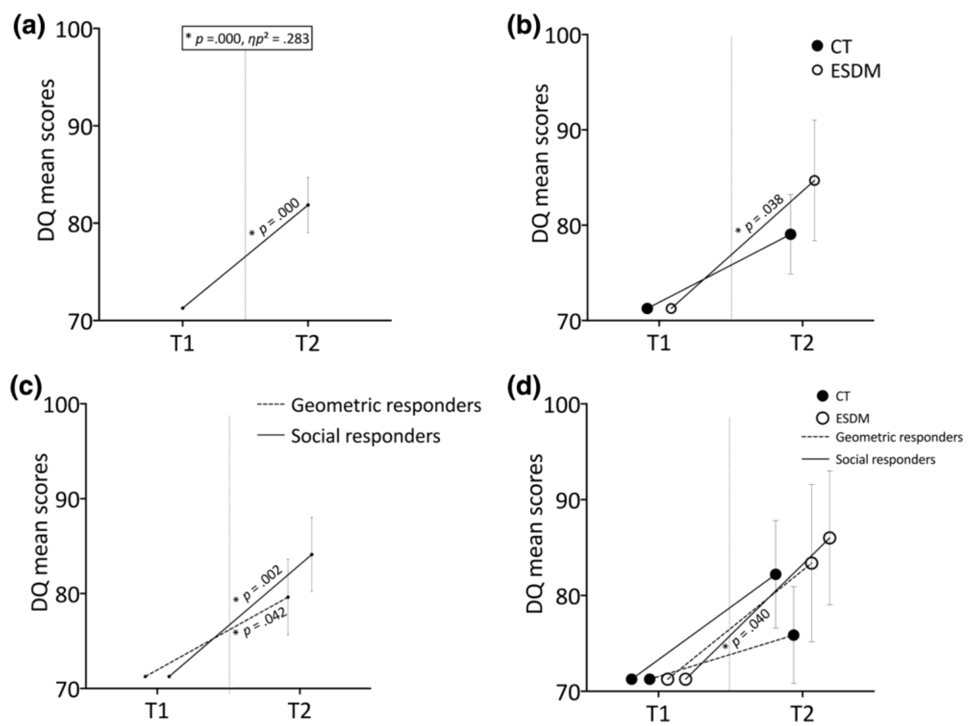


Fig. 4 Developmental Quotient changes over time, **a** DQ overall mean at baseline and after 1 year of intervention, **b** DQ mean at baseline and after 1 year of intervention by Intervention group (ESDM vs. CT) **c.** DQ mean at baseline and after 1 year of intervention by Social orienting group (Social responders vs. Geometric responders) **d** DQ mean at baseline and after 1 year of intervention in ESDMxGeo, ESDMxSoc, CTxGeo and CTxSoc. Baseline values represent the mean DQ while the changes represent the mean change for each group. Framed values represent results from the ANCOVA, values in the graphs represent pairwise comparisons

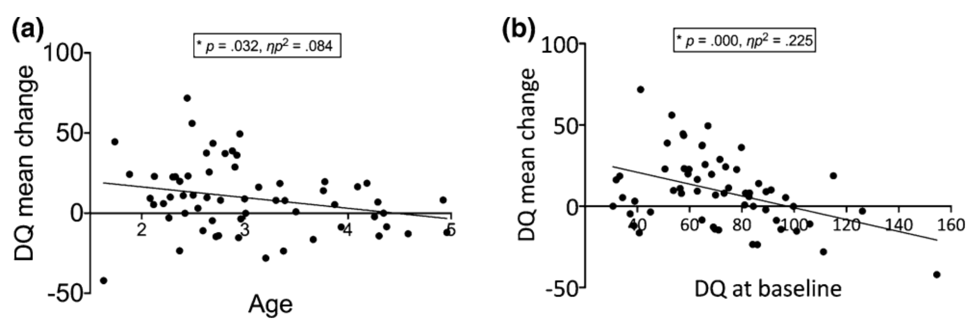


Fig. 5 Regressions between significant predictors and DQ change, **a** Age at baseline and DQ change, **b** DQ at baseline and DQ change

($p > 0.05$). A stepwise regression indicated that the combination of both predictors resulted in (F(2, 58) = 3585.335, $p < 0.001$) with an $R^2$ of 0.260. DQ change was equal to 62.228–8.083 (Age; SE = 3.057) − 0.396 (DQ at baseline; SE = 0.101). DQ change was best explained by DQ level at baseline ($R^2 = 0.169$, $p = 0.001$) followed by age at baseline ($R^2 = 0.091$, $p = 0.011$). There was no significant interaction between time and intervention group ($p > 0.05$), meaning that the mean DQ change over time were equivalent between CT and ESDM. Intervention groups did not differ in mean DQ scores at T1 and T2, despite a significant 6.328 ($p = 0.038$; see Fig. 4b) increase of DQ mean scores over time for children in the ESDM based intervention group. Regarding the social orienting groups, there was no interaction with time ($p > 0.05$; see Table 2; Fig. 4c). In addition, SR and GR groups did no show any differences at T1 and T2 regarding their mean DQ scores (all $p > 0.05$) but they both made significant increase after 1 year of intervention (SR = 12.841, $p = 0.002$; GR = 8.356, $p = 0.042$, see Fig. 4c).

Finally, there was no interaction between time, intervention group and social orienting group ($p > 0.05$; see Table 2; Fig. 4d). Pairwise comparison did not identify significant differences at baseline and after 1 year of intervention between groups (all $p > 0.05$) but there was a significant DQ increase of 4.441 ($p = 0.040$; see Fig. 4d) in children receiving ESDM based intervention group and being SR.

Finally, levels of maladaptive behaviors at baseline were significantly correlated and predictive of the DQ scores at baseline such lower maladaptive scores, i.e. more maladaptive behaviors ($r = 0.66$, $R^2 = 0.43$, $p < 0.001$; see Fig. 6a), were associated with lower DQ scores at baseline. In addition, we observed that levels of maladaptive behaviors at baseline were significantly correlated and predictive of the DQ scores after 1 year of intervention (T2) such lower maladaptive scores, i.e. more maladaptive behaviors ($r = 0.55$, $R^2 = 0.30$, $p < 0.001$; see Fig. 6b), were associated with lower DQ scores after 1 year of intervention. In other words, levels of maladaptive behaviors were predictive of cognitive scores both at baseline and after 1 year of intervention. However, we did not identify any relationship between the levels of maladaptive behaviors at baseline and the change in DQ over time ($r = -0.11$, $R^2 = 0.01$, $p > 0.05$; see Fig. 6c). These results suggest that despite a relationship between maladaptive behaviors and DQ scores, all children might experience a great change in DQ scores regardless of their initial levels of maladaptive behaviors. However, it appears that the children who experience the greater increase of their DQ scores over time are the ones who also greatly reduced their levels of maladaptive behaviors over time ($r = 0.36$, $R^2 = 0.13$, $p = 0.007$; see Fig. 6d).

An additional post-hoc power analysis was conducted using the software package, G*Power3 (Faul et al. 2007). The sample size of 60 was used for the statistical power analyses, number of groups was 4 and 8, when looking at main effects and interactions respectively, with 3 covariates included in the model and using an a of 0.05. The recommended effect sizes used for this assessment were as follows: small (f = 0.10), medium (f = 0.25), and large (f = 0.40) (Cohen 1988). The post hoc analyses revealed the statistical power for this study was 0.12 for detecting a small effect,

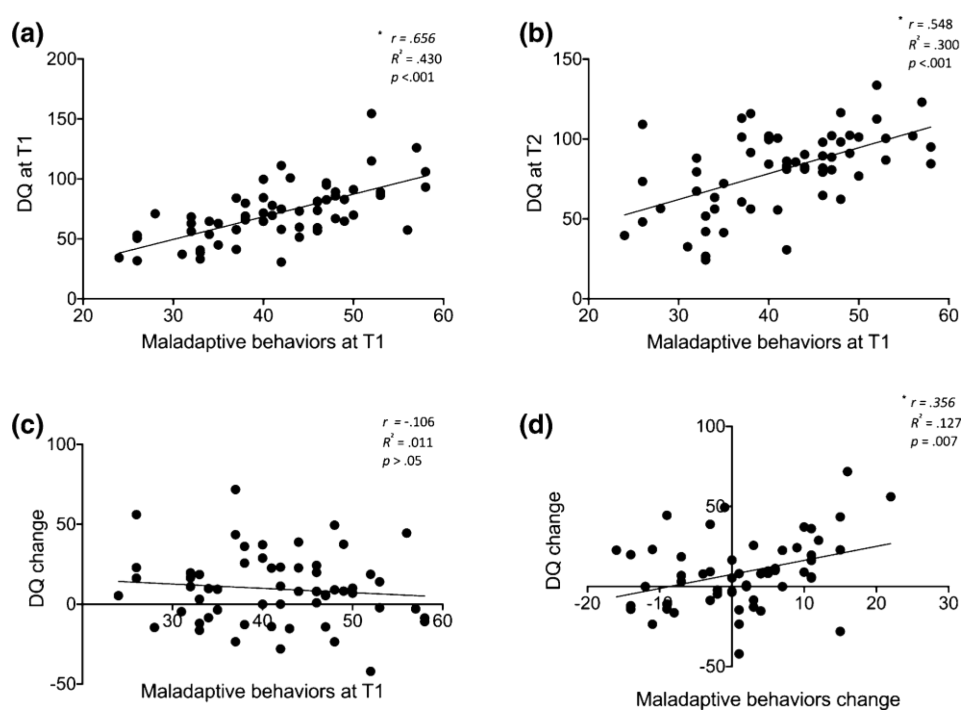


Fig. 6 Association between DQ and Maladaptive behaviors **a** Regression and correlation between Maladaptive behaviors and DQ scores at baseline; **b** Regression and correlation between Maladaptive behaviors scores at baseline and DQ scores at T2; **c** Regression and correlation between Maladaptive behaviors scores at baseline and DQ change over time; **d** Regression and correlation between Maladaptive behaviors and DQ changes over time

0.48 for detecting a medium effect and 0.86 for detecting a large effect size. In consequence, there was adequate power (> 0.80) at the large effect size level but not enough statistical power for the small to moderate effect size level. Additional power analysis using similar parameters showed that, in order to reach a power of 0.80 for small and medium effects, sample size should increase up to 787 and 128 participants respectively.

## Discussion

This study aimed to explore predictors of intervention outcome in a European context. In line with numerous studies advocating for early and intensive intervention, we observed that access to a comprehensive program, such as the ESDM, was the main predictor of decreased socio-communicative deficits after 1 year of intervention (Fig. 2b). Taken as individual factors, neither a higher number of hours nor a younger age at baseline showed a significant impact on outcome. This might suggest that, in order to be effective, an intervention should really combine both parameters. In addition, we observed that a gain in cognitive skills was best predicted by a combination of lower DQ and younger age at baseline (Fig. 5a, b). We estimate that this greater cognitive gain for children with lower DQ at baseline can be explained by the fact that they have a wider margin for progress. Furthermore, we hypothesize that better cognitive scores at follow-up could also rely on a reduction of maladaptive behaviors (Fig. 6). Finally, despite the fact that our main ANCOVA model did not identify social orienting as a significant predictor of outcome, results from our pairwise analyses suggest that social orienting had a meaningful impact on outcome. Indeed, only SR children showed a decrease in their autism symptoms (Fig. 3c), led by improvements in the social affect domain (Fig. 2c). Further, we observed that a child's social orienting potentiates the effect of early and intensive intervention; only the SR receiving ESDM showed significant autistic symptoms decline (Figs. 2d, 3d) or cognitive gains over time (Fig. 4d).

### Early and Intensive Intervention

Our results showed that receiving a comprehensive early and intensive intervention program (here, the ESDM) was the best predictor of ASD symptom decrease over time, providing further support for the well-established finding that early and intensive intervention is critical for therapeutic outcome (Elder et al. 2016; Eldevik et al. 2009; Fenske et al. 1985; Flanagan et al. 2012; French and Kennedy 2017; Klintwall et al. 2015; Linstead et al. 2017a, b; Mathews et al. 2018; Stahmer et al. 2019). However, our results do not bring support for higher number of hours of therapy as a standalone predictor of greater intervention outcome. This result is interesting considering that Rogers et al. (2012) suggested that interventions should combine both early and intensive factors in order to be effective. This combination of factors is supported by previous studies linking the larger gains occurring in early and intensive intervention with higher level of brain plasticity during critical developmental windows (Dawson 2008; Pascual-Leone et al. 2005; Sullivan et al. 2014). The importance of higher intensity of intervention during a critical developmental period have been supported by Granpeesheh et al. (2009) results who showed a positive relationship between the number of hours received and treatment outcome for children between 2-and- 5-years-of-age but not in children older than 7-years-old. Taken together, previous and present results suggest that, taken independently, a younger age at baseline or a more intensive intervention might have a moderated effect on outcome, whereas a combination of both factors together could have a stronger influence on outcome by taking advantage of critical developmental window. Finally, our results highlight specific improvement in social communication skills in the group receiving early and intensive intervention, but not in the CT group. We hypothesize that this specific gain might be associated with the specificity of ESDM intervention. Indeed, ESDM was developed as an ASD-specific intervention, targeting all areas of development, with a particular attention to social communication (e.g., joint attention, nonverbal communication and imitation Rogers and Dawson 2010) which is particularly altered in ASD (Mundy 1995; Thorup et al. 2018). ESDM is also a manualized, data-driven approach, where all therapists work in a systematic way to target common developmental objectives specific to the needs of the child. Emphasizing social communication in a coordinated and systematic way during a period of early brain development may be key to improving core symptoms of autism, whereas nonspecific interventions, such as those provided in the CT group, may target more transversal skills (such as language skills in a speech therapy; see Ganz and Simpson 2004) and have a more diffuse effect regarding core features of autism.

### Lower Cognitive Skills and Younger Age at Baseline are Associated with Greater Cognitive Gains Over Time

In the present study, we observed that children with lower cognitive levels at baseline showed larger gains in their cognitive abilities over time than children who had higher cognitive levels at baseline. While numerous studies report that children with higher cognitive scores at baseline are more likely to have a better outcome (Anderson et al. 2007; Fernell et al. 2011; Harris and Handleman 2000; Tiura et al. 2017), a meta-analysis by Reed (2016) suggests a more complex relationship between baseline IQ and cognitive gain. Similarly to our results, over the range between

50 and 80 of baseline IQ, Reed (2016) observed a negative relationship between baseline IQ and cognitive gain whereby children with the lowest baseline IQ scores showed the largest cognitive gain over time. As suggested by Reed (2016), this phenomenon could be explained by the fact that children with low cognitive functioning at baseline were also the ones with more potential progress, compared to children with high levels of cognitive functioning at baseline. In addition, we investigated if this larger cognitive gain observed in children with lower baseline functioning might be explained by improvement in their behavior and subsequent improvement in test-taking ability. Results from our Post-hoc analyses shown that before intervention, the level of maladaptive behaviors was predictive of DQ mean scores, whereby more maladaptive behaviors were associated with lower DQ, potentially because maladaptive behaviors impaired children's ability to follow instructions and respond adequately during testing. In addition, levels of maladaptive behaviors at baseline did not predict change in DQ, meaning that children with both high and low levels of maladaptive behaviors could improve their cognitive skills, while children showing a larger decrease in maladaptive behavior were the ones who had more cognitive gain over time. As such, we hypothesize that, at this age, reducing maladaptive behaviors may results in substantial cognitive gains through the improvement of test-taking ability. These results are also consistent with several studies reporting a relationship between lower IQ and the presence of more maladaptive behaviors (Shattuck et al. 2007; Woodman et al. 2015), even within a non-autistic population (Ando and Yoshimura 1978).

## Social Orienting: A Potential Outcome Contributor

Finally, we did not find social orienting at baseline to be a significant predictor of outcome. However, our results suggest that levels of social orientating at baseline may predict dissimilar symptom patterns between subgroups, whereby children who preferred geometric stimuli tended to have increased levels of RRB symptoms and children who preferred the biological stimuli showed a decrease in levels of SA symptoms 1 year after the start of intervention. These results are in line with previous studies looking at developmental trajectories using similar tools (Franchini et al. 2016, 2018; Pierce et al. 2011). Franchini et al. (2016) showed that Social Responders tended to increase their social abilities, resulting in a decrease in their autistic symptoms after 1 year of intervention, whereas Geometric Responders tended to stay stable or show an increase in their autistic symptoms. Our results support the social motivation theory (Chevallier et al. 2012a, b; Dawson 2008; Klin et al. 2002; Mundy 1995), which describes the idea that a deficit in early socialattention has a cascading effect on a child with autism's development, leading to autistic symptomatology. Indeed, typically developing children have been shown to automati- cally orient to social cues during early childhood (Morrisey et al. 2018), whereas children with ASD appear to orient less to these cues (Franchini et al. 2016; Jones et al. 2014; Jones and Klin 2013; Morrisey et al. 2018; Pierce et al. 2011, 2016). The reason for this early difference is commonly explained by a lack of reward perceived from social cues for individuals with ASD (Chevallier et al. 2012a, b). Consequently, as children with ASD pay less attention to social cues, they may also miss learning opportunities (Dawson et al. 1998; Franchini et al. 2019). As with previously cited studies, our results support the idea that children who showed more interest in social stimuli before intervention had a faster rate of improvement in their social communication skills, whereas children who were mostly attracted by the geometric stimuli at baseline showed an increase in repetitive behaviors over time, potentially leading them to miss crucial learning opportunities while their attention was more focused on non-social stimuli. Furthermore, our results showed that, despite a non-significant interaction between type of intervention and social orienting group factors, the only group of children making significant progress on both ASD symptomatology and cognitive levels were the ones receiving an early and intensive intervention program, and who were already Social Responders at baseline. Children receiving similar intervention but who were Geometric Responders improved their ASD symptoms but at a slower pace, and did not reach significance criteria. On a speculative basis, we could extend these results to the question of "*timing of treatment response*" raised by Vivanti et al. (2014), in their theoretical paper. Vivanti et al. (2014) high- lighted the lack of knowledge regarding the timing of treatment response and questioned whether or not children who do not respond to an intervention during the first year would show significant changes during the following year. We thus speculate that SR at baseline would show an earlier response to treatment, especially in an ESDM based intervention which emphasizes the importance of social engagement as a main principle intervention (Rogers and Dawson 2010) as the SR child may be more inclined to engage in social interactions compared to a GR child. In line with this hypothesis, GR children might take more time to benefit from the intervention, as they are less likely to socially engage at baseline. Consequently, increasing their social orienting level as a first step of intervention might elicit better subsequent progress in the following period, which could be confirmed by further exploring the association between both parameters (Type of intervention × SO) over an extended time frame.

## Limitations

One limitation of our study is that our sample includes only males with ASD. We chose to exclusively include males for multiple reasons. First, autism affects more males than females, with a sex ratio of approximately 4:1 (Christensen et al. 2016). While we could have included females with an equivalent sex ratio of 4:1, important phenotype differences (Frazier et al. 2014) including more difficulties in social communication, lower cognitive abilities, less-restricted interests and less-developed adaptive behaviors in females, as well as subjacent genetic differences (Chen et al. 2017) were identified within literature between males and females. Considering these sex differences, we chose to exclude females from our sample to avoid any misleading effects that could arise from this sex-specific phenotype.

Another limitation lies in our statistical analyses, which involved only a limited sample size, as illustrated by our power analysis described above. These analyses showed that a bigger sample size, up to 787 participants, may be needed in order to reach high statistical power for small effect size, which is way beyond the number of participants currently included in our longitudinal protocol. Consequently, and despite our efforts for controlling for covariates and to apply multiple comparisons correction, these results should be considered with caution and preliminary.

Moreover, we decided to focus our analyses on a set of selected predictors, but many other predictors could have been explored, such as parental implication for example (Chen et al. 2017; Narzisi et al. 2015). Similarly, other outcome measures could have been taken into consideration, such as quality of life, as suggested by Bieleninik et al. (2017), necessary skills for future functioning or stress reduction, as suggested by parents reviewed by McConachie et al. (2018). We chose our predictors because most of them were widely acknowledged throughout the literature but not yet in a European context. However, future research should explore alternative predictors and outcome variables.

While observational studies might bring a more naturalistic assessment of the outcome of currently available interventions compared to RCT, many parameters remained uncontrolled and unmatched (e.g., hours of treatment) between our intervention groups. As a result, our results should not be used to praise for any intervention (ESDM vs. CT).

Finally, as mentioned in the Method section, raters were not blind to the intervention received but did not take part in the intervention. In the context of our study, blinding was not possible for the examiners, as issues related to the type and intensity of intervention often came up in discussions with the families (e.g. when scheduling appointments, or when families ask for advices). While some prospective studies have achieved blinding by hiring a naïve rater who assessed the children at several timepoints (see Bieleninik et al. 2017 for a review), we did not consider this when we started this study.

## Conclusion

The present study brings additional support for early and intensive intervention to reduce autistic symptoms and improve cognitive levels. The importance of improving early screening for ASD and increasing access to comprehensive early intervention programs in Europe is evident. Furthermore, this study showed that cognitive gains over time are mostly demonstrated by children with lower cognitive levels at baseline, especially when maladaptive behaviors are reduced over time. Finally, this study provides support for the use of eye-tracking as a promising tool to distinguish between subgroups of children who might show different trajectories of their autistic symptoms over time and who respond differentially to specific types of intervention. Our study provided preliminary data suggesting that children who are more socially engaged at baseline might respond faster to interventions which emphasize socio-communicative interaction, compared to children who are less interested in social stimuli. Further studies should explore whether or not increasing social orienting is associated with subsequent clinical improvement over time.

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## Compliance with Ethical Standards

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or the National Research Committee, as well as with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from the parents of all participants included in the study.

## Reference


American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5* (5th ed.). American Psychiatric Association: Washington, DC.

Anderson, D. K., Lord, C., Risi, S., DiLavore, P. S., Shulman, C., Thurm, A., et al. (2007). Patterns of growth in verbal abilities among children with autism spectrum disorder. *Journal of Consulting and Clinical Psychology, 75*(4), 594–604. https://doi.org/10.1037/0022-006X.75.4.594.

Ando, H., & Yoshimura, I. (1978). Prevalence of maladaptive behavior in retarded children as a function of IQ and age. *Journal of Abnormal Child Psychology, 6*(3), 345–349.

Benvenuto, A., Battan, B., Benassi, F., Gialloreti, L. E., & Curatolo, P. (2016). Effectiveness of community-based treatment on clinical outcome in children with autism spectrum disorders: An Italian prospective study. *Developmental Neurorehabilitation, 19*(1), 1–9. https://doi.org/10.3109/17518423.2013.864716.

Bieleninik, Ł., Posserud, M.-B., Geretsegger, M., Thompson, G., Elefant, C., & Gold, C. (2017). Tracing the temporal stability of autism spectrum diagnosis and severity as measured by the Autism Diagnostic Observation Schedule: A systematic review and meta-analysis. *PLoS ONE, 12*(9), e0183160. https://doi.org/10.1371/journal.pone.0183160.

Chen, C., Van Horn, J. D., & GENDAAR Research Consortium. (2017). Developmental neurogenetics and multimodal neuroimaging of sex differences in autism. *Brain Imaging and Behavior, 11*(1), 38–61. https://doi.org/10.1007/s11682-015-9504-3.

Chevallier, C., Grèzes, J., Molesworth, C., Berthoz, S., & Happé, F. (2012a). Brief report: Selective social anhedonia in high functioning autism. *Journal of Autism and Developmental Disorders, 42*(7), 1504–1509. https://doi.org/10.1007/s10803-011-1364-0.

Chevallier, C., Kohls, G., Troiani, V., Brodkin, E. S., & Schultz, R. T. (2012b). The social motivation theory of autism. *Trends in Cognitive Sciences, 16*(4), 231–239. https://doi.org/10.1016/j.tics.2012.02.007.

Christensen, D. L., Bilder, D. A., Zahorodny, W., Pettygrove, S., Durkin, M. S., Fitzgerald, R. T., et al. (2016). Prevalence and characteristics of autism spectrum disorder among 4-year-old children in the autism and developmental disabilities monitoring network. *Journal of Developmental & Behavioral Pediatrics, 37*(1), 1–8. https://doi.org/10.1097/DBP.0000000000000235.

Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). Hillsdale, NJ: Lawrence Earlbaum Associates.

Colombi, C., Narzisi, A., Ruta, L., Cigala, V., Gagliano, A., Pioggia, G., et al. (2016). Implementation of the Early Start Denver Model in an Italian community. *Autism, 22*(2), 126–133. https://doi.org/10.1177/1362361316665792.

Darrou, C., Pry, R., Pernon, E., Michelon, C., Aussilloux, C., & Baghdadli, A. (2010). Outcome of young children with autism: Does the amount of intervention influence developmental trajectories? *Autism, 14*(6), 663–677. https://doi.org/10.1177/1362361310374156.

Dawson, G. (2008). Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. *Development and Psychopathology, 20*(3), 775–803. https://doi.org/10.1017/S0954579408000370.

Dawson, G., Meltzoff, A. N., Osterling, J., Rinaldi, J., & Brown, E. (1998). Children with autism fail to orient to naturally occurring social stimuli. *Journal of Autism and Developmental Disorders, 28*(6), 479–485. https://doi.org/10.1023/a:1026043926488.

Dawson, G., Rogers, S., Munson, J., Smith, M., Winter, J., Greenson, J., et al. (2010). Randomized, controlled trial of an intervention for toddlers with autism: The Early Start Denver Model. *Pediatrics, 125*(1), e17–e23. https://doi.org/10.1542/peds.2009-0958.

Elder, J. H., Brasher, S., & Alexander, B. (2016). Identifying the barriers to early diagnosis and treatment in underserved individuals with autism spectrum disorders (ASD) and their families: A qualitative study. *Issues in Mental Health Nursing, 37*(6), 412–420. https://doi.org/10.3109/01612840.2016.1153174.

Eldevik, S., Hastings, R. P., Hughes, J. C., Jahr, E., Eikeseth, S., & Cross, S. (2009). Meta-analysis of early intensive behavioral intervention for children with autism. *Journal of Clinical Child and Adolescent Psychology, 38*(3), 439–450. https://doi.org/10.1080/15374410902851739.

Faul, F., Erdfelder, E., Lang, A.-G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*, 175–191.

Fenske, E. C., Zalenski, S., Krantz, P. J., & McClannahan, L. E. (1985). Age at intervention and treatment outcome for autistic children in a comprehensive intervention program. *Analysis and Intervention in Developmental Disabilities, 5*, 49–58.

Fernell, E., Hedvall, Å., Westerlund, J., Höglund Carlsson, L., Eriksson, M., Barnevik Olsson, M., et al. (2011). Early intervention in 208 Swedish preschoolers with autism spectrum disorder: A prospective naturalistic study. *Research in Developmental Disabilities, 32*(6), 2092–2101. https://doi.org/10.1016/j.ridd.2011.08.002.

Flanagan, H. E., Perry, A., & Freeman, N. L. (2012). Effectiveness of large-scale community-based intensive behavioral intervention: A waitlist comparison study exploring outcomes and predictors. *Research in Autism Spectrum Disorders, 6*(2), 673–682. https://doi.org/10.1016/j.rasd.2011.09.011.

Franchini, M., Armstrong, V. L., Schaer, M., & Smith, I. M. (2019). Initiation of joint attention and related visual attention processes in infants with autism spectrum disorder: Literature review. *Child Neuropsychology, 25*(3), 287–317. https://doi.org/10.1080/09297049.2018.1490706.

Franchini, M., Glaser, B., Wood de Wilde, H., Gentaz, E., Eliez, S., & Schaer, M. (2017). Social orienting and joint attention in preschoolers with autism spectrum disorders. *PLoS ONE, 12*(6), e0178859. https://doi.org/10.1371/journal.pone.0178859.

Franchini, M., Wood de Wilde, H., Glaser, B., Gentaz, E., Eliez, S., & Schaer, M. (2016). Brief report: A preference for biological motion predicts a reduction in symptom severity 1 year later in preschoolers with autism spectrum disorders. *Frontiers in Psychiatry, 7*, 143. https://doi.org/10.3389/fpsyt.2016.00143.

Franchini, M., Zöller, D., Gentaz, E., Glaser, B., Wood de Wilde, H., Kojovic, N., et al. (2018). Early adaptive functioning trajectories in preschoolers with autism spectrum disorders. *Journal of Pediatric Psychology., 43*(7), 800–813. https://doi.org/10.1093/jpepsy/jsy024.

Frazier, T. W., Georgiades, S., Bishop, S. L., & Hardan, A. Y. (2014). Behavioral and cognitive characteristics of females and males with autism in the Simons Simplex Collection. *Journal of the American Academy of Child and Adolescent Psychiatry, 53*(3), 329–340.e3. https://doi.org/10.1016/j.jaac.2013.12.004.

Freitag, C. M., Feineis-Matthews, S., Valerian, J., Teufel, K., & Wilker, C. (2012). The Frankfurt early intervention program FFIP for preschool aged children with autism spectrum disorder: A pilot study. *Journal of Neural Transmission, 119*(9), 1011–1021. https://doi.org/10.1007/s00702-012-0792-0.

French, L., & Kennedy, E. M. (2017). Annual research review: Early intervention for infants and young children with, or at-risk of, autism spectrum disorder: A systematic review. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 59*, 444–456. https://doi.org/10.1111/jcpp.12828.

Ganz, J. B., & Simpson, R. L. (2004). Effects on communicative requesting and speech development of the Picture Exchange Communication System in children with characteristics of autism. *Journal of Autism and Developmental Disorders, 34*(4), 395–409.

Gotham, K., Pickles, A., & Lord, C. (2009). Standardizing ADOS scores for a measure of severity in autism spectrum disorders. *Journal of Autism and Developmental Disorders, 39*(5), 693–705. https://doi.org/10.1007/s10803-008-0674-3.

Granpeesheh, D., Dixon, D. R., Tarbox, J., Kaplan, A. M., & Wilke, A. E. (2009). The effects of age and treatment intensity on behavioral intervention outcomes for children with autism spectrum disorders. *Research in Autism Spectrum Disorders, 3*(4), 1014–1022. https://doi.org/10.1016/j.rasd.2009.06.007.

Green, J., Pickles, A., Pasco, G., Bedford, R., Wan, M. W., & Elsabbagh, M. (2017). Randomised trial of a parent-mediated intervention for infants at high risk for autism: Longitudinal outcomes to age 3 years. *Journal of Child Psychology and Psychiatry, and Allied Disciplines, 58*(12), 1330–1340. https://doi.org/10.1111/jcpp.12728.

Harris, S. L., & Handleman, J. S. (2000). Age and IQ at intake as predictors of placement for young children with autism: A four- to six-year follow-up. *Journal of Autism and Developmental Disorders, 30*(2), 137–142.

Hus, V., Gotham, K., & Lord, C. (2014). Standardizing ADOS domain scores: Separating severity of social affect and restricted and repetitive behaviors. *Journal of Autism and Developmental Disorders, 44*(10), 2400–2412. https://doi.org/10.1007/s10803-012-1719-1.

Jones, E. J. H., Gliga, T., Bedford, R., Charman, T., & Johnson, M. H. (2014). Developmental pathways to autism: A review of prospective studies of infants at risk. *Neuroscience and Biobehavioral Reviews, 39*(100), 1–33. https://doi.org/10.1016/j.neubiorev.2013.12.001.

Jones, W., & Klin, A. (2013). Attention to eyes is present but in decline in 2–6-month-old infants later diagnosed with autism. *Nature, 504*(7480), 427. https://doi.org/10.1038/nature12715.

Kasari, C., Freeman, S., & Paparella, T. (2006). Joint attention and symbolic play in young children with autism: A randomized controlled intervention study. *Journal of Child Psychol- ogy and Psychiatry, 47*(6), 611–620. https://doi.org/10.1111/j.1469-7610.2005.01567.x.

Kasari, C., Gulsrud, A., Freeman, S., Paparella, T., & Hellemann, G. (2012). Longitudinal follow-up of children with autism receiving targeted interventions on joint attention and play. *Journal of the American Academy of Child and Adolescent Psychiatry, 51*(5), 487–495. https://doi.org/10.1016/j.jaac.2012.02.019.

Kawabe, K., Kondo, S., Matsumoto, M., Seo, K., Ochi, M., Oka, Y., et al. (2016). Developmental quotient to estimate intelligence in autism spectrum disorder. *Pediatrics International, 58*(10), 963–966. https://doi.org/10.1111/ped.12969.

Klin, A., Jones, W., Schultz, R., Volkmar, F., & Cohen, D. (2002). Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. *Archives of General Psychiatry, 59*(9), 809–816. https://doi.org/10.1001/archpsyc.59.9.809.

Klintwall, L., Eldevik, S., & Eikeseth, S. (2015). Narrowing the gap: Effects of intervention on developmental trajectories in autism, Narrowing the gap: Effects of intervention on developmental trajectories in autism. *Autism, 19*(1), 53–63. https://doi.org/10.1177/1362361313510067.

Koegel, L. K., Koegel, R. L., Harrower, J. K., & Carter, C. M. (1999). Pivotal response intervention I: Overview of approach. *Research and Practice for Persons with Severe Disabilities, 24*(3), 174–185. https://doi.org/10.2511/rpsd.24.3.174.

Landa, R. J., Stuart, E. A., Gross, A. L., & Faherty, A. (2013). Developmental trajectories in children with and without autism spectrum disorders: The first 3 years. *Child Development, 84*(2), 429–442. https://doi.org/10.1111/j.1467-8624.2012.01870.x.

Linstead, E., Dixon, D. R., French, R., Granpeesheh, D., Adams, H., German, R., et al. (2017a). Intensity and learning outcomes in the treatment of children with autism spectrum disorder. *Behavior Modification, 41*(2), 229–252. https://doi.org/10.1177/0145445516667059.

Linstead, E., Dixon, D. R., Hong, E., Burns, C. O., French, R., Novack, M. N., & Granpeesheh, D. (2017b). An evaluation of the effects of intensity and duration on outcomes across treatment domains for children with autism spectrum disorder. *Translational Psychiatry, 7*(9), e1234. https://doi.org/10.1038/tp.2017.207.

Lord, C., Risi, S., Lambrecht, L., Cook, E. H., Leventhal, B. L., DiLavore, P. C., et al. (2000). The autism diagnostic observation schedule-generic: A standard measure of social and communication deficits associated with the spectrum of autism. *Journal of Autism and Developmental Disorders, 30*(3), 205–223.

Lord, C., Rutter, M., DiLavore, P. C., Risi, S., Gotham, K., & Bishop, S. L. (2012). *Autism diagnostic observation schedule, 2nd edition (ADOS-2)*. Western Psychological Services: Vancouver.

Lovaas, O. I., Schreibman, L., & Koegel, R. L. (1974). A behavior modification approach to the treatment of autistic children. *Journal of Autism and Childhood Schizophrenia, 4*(2), 111–129. https://doi.org/10.1007/BF02105365.

Mathews, T., Lugo, A., King, M., Needelman, L., McArdle, P., Romer, N., et al. (2018). Expanding access to clinical services for toddlers with autism spectrum disorders. *Journal of Pediatric Health Care, 32*(2), 173–183. https://doi.org/10.1016/j.pedhc.2017.09.011.

McConachie, H., Livingstone, N., Morris, C., Beresford, B., Couteur, A. L., Gringras, P., et al. (2018). Parents suggest which indicators of progress and outcomes should be measured in young children with autism spectrum disorder. *Journal of Autism and Developmental Disorders, 48*(4), 1041–1051. https://doi.org/10.1007/s10803-017-3282-2.

Morrisey, M. N., Reed, C. L., McIntosh, D. N., & Rutherford, M. D. (2018). Brief report: Attentional cueing to images of social interactions is automatic for neurotypical individuals but not those with ASC. *Journal of Autism and Developmental Disorders*. https://doi.org/10.1007/s10803-018-3592-z.

Motulsky, H. J., & Brown, R. E. (2006). Detecting outliers when fitting data with nonlinear regression: A new method based on robust nonlinear regression and the false discovery rate. *BMC Bioinformatics, 7*, 123. https://doi.org/10.1186/1471-2105-7-123.

Mundy, P. (1995). Joint attention and social-emotional approach behavior in children with autism. *Development and Psychopathology, 7*(1), 63–82. https://doi.org/10.1017/S0954579400006349.

Narzisi, A., Muratori, F., Buscema, M., Calderoni, S., & Grossi, E. (2015). Outcome predictors in autism spectrum disorders preschoolers undergoing treatment as usual: Insights from an observational study using artificial neural networks. *Neuropsychiatric Disease and Treatment, 11*, 1587–1599. https://doi.org/10.2147/NDT.S81233.

National Research Council. (2001). *Educating children with autism*. Washington DC: National Academies Press.

Pascual-Leone, A., Amedi, A., Fregni, F., & Merabet, L. B. (2005). The plastic human brain cortex. *Annual Review of Neuroscience, 28*(1), 377–401. https://doi.org/10.1146/annurev.neuro.27.070203.144216.

Pierce, K., Conant, D., Hazin, R., Stoner, R., & Desmond, J. (2011). Preference for geometric patterns early in life as a risk factor for autism. *Archives of General Psychiatry, 68*(1), 101–109. https://doi.org/10.1001/archgenpsychiatry.2010.113.

Pierce, K., Marinero, S., Hazin, R., McKenna, B., Barnes, C. C., & Malige, A. (2016). Eye tracking reveals abnormal visual preference for geometric images as an early biomarker of an autism spectrum disorder subtype associated with increased symptom severity. *Biological Psychiatry, 79*(8), 657–666. https://doi.org/10.1016/j.biopsych.2015.03.032.

Polyak, A., Kubina, R. M., & Girirajan, S. (2015). Comorbidity of intellectual disability confounds ascertainment of autism: Implications for genetic diagnosis. *American Journal of Medical Genetics, 168*(7), 600–608. https://doi.org/10.1002/ajmg.b.32338.

Prizant, B. M., Wetherby, A. M., Rubin, E., Laurent, A. C., & Rydell, P. (2006). *The scerts model: A comprehensive educational approach for children with autism spectrum disorders*. Baltimore: Brookes Publishing Co.

Maw, S.S., & Haga, C. (2018). Effectiveness of cognitive, developmental, and behavioural interventions for Autism Spectrum Disorder in preschool-aged children: A systematic review and meta-analysis. *Heliyon, 4*(9), e00763. https://doi.org/10.1016/j.heliyon.2018.e00763.

Reed, P. (2016). *Interventions for autism: Evidence for educational and clinical practice*. Hoboken: Wiley.

Reichow, B. (2012). Overview of meta-analyses on early intensive behavioral intervention for young children with autism spectrum disorders. *Journal of Autism and Developmental Disorders, 42*(4), 512–520. https://doi.org/10.1007/s10803-011-1218-9.

Remington, B., Hastings, R. P., & Kovshoff, H. (2007). Early intensive behavioral intervention: Outcomes for children with autism and their parents after two years. *American Journal on Mental Retardation, 112*(6), 418–438. https://doi.org/10.1352/0895-8017(2007)112[418:EIBIOF]2.0.CO;2.

Rogers, S., & Dawson, G. (2010). *Early Start Denver Model for young children with autism: Promoting language, learning, and engagement*. New York: Guilford Press.

Rogers, S., Estes, A., Lord, C., Vismara, L., Winter, J., Fitzpatrick, A., et al. (2012). Effects of a Brief Early Start Denver Model (ESDM)–based parent intervention on toddlers at risk for autism spectrum disorders: A randomized controlled trial. *Journal of the American Academy of Child & Adolescent Psychiatry, 51*(10), 1052–1065. https://doi.org/10.1016/j.jaac.2012.08.003.

Rogers, S., Vismara, L., Wagner, A. L., McCormick, C., Young, G., & Ozonoff, S. (2014). Autism treatment in the first year of life: A pilot study of infant start, a parent-implemented intervention for symptomatic infants. *Journal of Autism and Developmental Disorders, 44*(12), 2981–2995. https://doi.org/10.1007/s10803-014-2202-y.

Rosenbaum, P. (2010). The randomized controlled trial: An excellent design, but can it address the big questions in neurodisability? *Developmental Medicine & Child Neurology, 52*(2), 111–111. https://doi.org/10.1111/j.1469-8749.2009.03557.x.

Salomone, E., Beranová, Š., Bonnet-Brilhault, F., Briciet Lauritsen, M., Budisteanu, M., Buitelaar, J., et al. (2016). Use of early intervention for young children with autism spectrum disorder across Europe. *Autism, 20*(2), 233–249. https://doi.org/10.1177/1362361315577218.

Salt, J., Sellars, V., Shemilt, J., Boyd, S., Coulson, T., & McCool, S. (2001). The Scottish Centre for autism preschool treatment programme: I: A developmental approach to early intervention. *Autism, 5*(4), 362–373. https://doi.org/10.1177/1362361301005004003.

Schietecatte, I., Roeyers, H., & Warreyn, P. (2011). Can infants' orientation to social stimuli predict later joint attention skills? *British Journal of Developmental Psychology, 30*(2), 267–282. https://doi.org/10.1111/j.2044-835X.2011.02039.x.

Schopler, E., Lansing, M., Reichler, R., & Marcus, L. (2005). *Psychoeducational Profile: TEACCH individualized assessment for children with autism spectrum disorders* (3rd ed.). Pro-Ed Inc: Austin.

Schreibman, L., Dawson, G., Stahmer, A., Landa, R., Rogers, S., McGee, G., et al. (2015). Naturalistic developmental behavioral interventions: Empirically validated treatments for autism spectrum disorder. *Journal of Autism and Developmental Disorders, 45*(8), 2411–2428. https://doi.org/10.1007/s10803-015-2407-8.

Shattuck, P. T., Seltzer, M. M., Greenberg, J. S., Orsmond, G. I., Bolt, D., Kring, S., et al. (2007). Change in autism symptoms and maladaptive behaviors in adolescents and adults with an autism spectrum disorder. *Journal of Autism and Developmental Disorders, 37*(9), 1735–1747. https://doi.org/10.1007/s10803-006-0307-7.

Stahmer, A. C., Vejnoska, S., Iadarola, S., Straiton, D., Segovia, F. R., Luelmo, P., et al. (2019). Caregiver voices: Cross-cultural input on improving access to autism services. *Journal of Racial and Ethnic Health Disparities., 6*(4), 752–773. https://doi.org/10.1007/s40615-019-00575-y.

Sullivan, K., Stone, W., & Dawson, G. (2014). Potential neural mechanisms underlying the effectiveness of early intervention for children with autism spectrum disorder. *Research in Developmental Disabilities, 35*(11), 2921–2932. https://doi.org/10.1016/j.ridd.2014.07.027.

Thorup, E., Nyström, P., Gredebäck, G., Bölte, S., Falck-Ytter, T., & Team the E. (2018). Reduced alternating gaze during social interaction in infancy is associated with elevated symptoms of autism in toddlerhood. *Journal of Abnormal Child Psychology, 46*(7), 1547–1564. https://doi.org/10.1007/s10802-017-0388-0.

Tiura, M., Kim, J., Detmers, D., & Baldi, H. (2017). Predictors of longitudinal ABA treatment outcomes for children with autism: A growth curve analysis. *Research in Developmental Disabilities*, *70*(Supplement C), 185–197. https://doi.org/10.1016/j.ridd.2017.09.008

Touzet, S., Occelli, P., Schröder, C., Manificat, S., Gicquel, L., Stanciu, R., et al. (2017). Impact of the Early Start Denver Model on the cognitive level of children with autism spectrum disorder: Study protocol for a randomised controlled trial using a two-stage Zelen design. *British Medical Journal Open, 7*(3), e014730. https://doi.org/10.1136/bmjopen-2016-014730.

Ventola, P. E., Oosting, D., Anderson, L. C., & Pelphrey, K. A. (2013). Chapter 10 - Brain mechanisms of plasticity in response to treatments for core deficits in autism. In M. M. Merzenich, M. Nahum, & T. M. Van Vleet (Eds.), *Progress in brain research* (Vol 207, pp. 255–272). Elsevier: Amsterdam.

Vivanti, G., Dissanayake, C., Zierhut, C., Rogers, S., & Team, V. A. (2013). Brief report: Predictors of outcomes in the early Start Denver Model Delivered in a group setting. *Journal of Autism and Developmental Disorders, 43*(7), 1717–1724. https://doi.org/10.1007/s10803-012-1705-7.

Vivanti, G., Prior, M., Williams, K., & Dissanayake, C. (2014). Predictors of outcomes in autism early intervention: Why don't we know more? *Frontiers in Pediatrics, 2*, 58. https://doi.org/10.3389/fped.2014.00058.

Woodman, A. C., Smith, L. E., Greenberg, J. S., & Mailick, M. R. (2015). Change in autism symptoms and maladaptive behaviors in adolescence and adulthood: The role of positive family processes. *Journal of Autism and Developmental Disorders, 45*(1), 111–126. https://doi.org/10.1007/s10803-014-2199-2.

Worrall, J. (2007). Why there's no cause to randomize. *The British Journal for the Philosophy of Science, 58*(3), 451–488. https://doi.org/10.1093/bjps/axm024.

Zwaigenbaum, L., Bauman, M. L., Choueiri, R., Kasari, C., Carter, A., Granpeesheh, D., et al. (2015). Early intervention for children with autism spectrum disorder under 3 years of age: Recommendations for practice and research. *Pediatrics, 136*(Supplement 1), S60–S81. https://doi.org/10.1542/peds.2014-3667E.

## 6.2 Full length article: Study 2

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# Distinct Patterns of Cognitive Outcome in Young Children With Autism Spectrum Disorder Receiving the Early Start Denver Model

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Evidence-based, early intervention significantly improves developmental outcome in young children with autism. Nonetheless, there is high interindividual heterogeneity in developmental trajectories during the therapy. It is established that starting intervention as early as possible results in better developmental outcomes. But except for younger age at start, there is no clear consensus about behavioral characteristics that could provide a reliable individual prediction of a child's developmental outcome after receiving an early intervention. In this study, we analyze developmental trajectories of preschoolers with autism who received 2 years of intervention using the Early Start Denver Model (ESDM) approach in Geneva, Switzerland in an individual setting ($n = 55$, aged $28.7 \pm 5.1$ months with a range of 15–42). Our aim was to identify early predictors of response to intervention. We applied a cluster analysis to distinguish between 3 groups based on their cognitive level at intake, and rates of cognitive change over the course of intervention. The first group of children only had a mild cognitive delay at intake and nearly no cognitive delay by the end of intervention (Higher Cognitive at baseline: HC). The children in the two other groups all presented with severe cognitive delay at baseline. However, they had two very different patterns of response to intervention. The majority significantly improved developmental scores over the course of intervention (Optimal Responders: OptR) whereas a minority of children showed only modest improvement (Minimal Responders: MinR). Further analyses showed that children who ended up having an optimal 2-year intervention outcome (OptR) were characterized by higher adaptive functioning at baseline combined with rapid developmental improvement during the first 6 months of intervention. Inversely, less significant progress by the sixth month of intervention was associated with a less optimal response to treatment (MinR).

Keywords: autism spectrum disorders, early intervention, predictors, response to treatment, heterogeneity, minimal responder



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## INTRODUCTION

Autism spectrum disorder (ASD) is characterized by impairments in communication and social interactions, along with restricted and repetitive behaviors (1). Over the last three decades, several comprehensive, evidence-based early intervention (EI) approaches have been developed for young children with ASD, with the aim to improve their social communication, cognitive functioning, and adaptive skills (2–7). The principles of EI usually comprise a significant number of hours (usually more than 15 h per week) as well as an early age of onset (usually younger than 4 or 5 years old) (8). Systematic reviews and meta-analyses showed positive effects of EI on cognition, adaptive skills and communication at the group level (9, 10). Nevertheless, many EI studies have reported a relatively heterogeneous response to these interventions, where most children show significant improvements, while others make smaller gains (11, 12). Despite important efforts to better understand variables affecting treatment response, it is currently not possible to predict to what extent a child will respond to intervention based on his or her behavioral characteristics at intake (13). In the current therapeutic context and in the absence of additional knowledge about individual predictors of outcome, many authors suggest that intensive early intervention should be an intervention of choice for young children diagnosed with ASD (14, 15) regardless of their specific behavioral or symptom profile. Yet, in the global framework of precision medicine (16), there is an urge to develop more individualized guidelines for intervention in ASD. Given the importance of providing effective programs for children with ASD as early as possible, and because of the costs and parental investment associated with early intervention, it is crucial that we move away from a "one size fits all" service provision model, and find ways to tailor a child's intervention to their specific needs, choosing therapy approaches based on the child's individual profile at diagnosis (17–19).

During the last decade, Early Start Denver Model (ESDM) has emerged as a promising Naturalistic Developmental Behavioral Interventions (NDBI) (7). NDBIs represent a category within the broader context of EIs, as discussed by Vivanti and Stahmer (20). Briefly, NDBIs designates approaches that integrate the methods derived from behavioral learning and developmental science. Main principles include varying the stimuli for learning, using the activities the child enjoys the most and emphasis put on developmental prerequisites. Within NDBIs, ESDM is notably characterized by its overall effectiveness, its emphasis on natural environment teaching, comprehensive learning objectives and parental involvement. ESDM intervention has originally been implemented in an individualized setting (one therapist for one child, I-ESDM), but other applications have been developed such as G-ESDM where one therapist works with a little group of children and P-ESDM where parents/caregivers actually provide the intervention under supervision. In their 2010 landmark randomized controlled trial (RCT) (2), Rogers and Dawson reported a mean increase of 18 IQ points in a sample of 24 toddlers with ASD receiving the I-ESDM intervention over 2 years. Numerous studies have replicated these results [for a review see (10)], highlighted a good reproducibility in different contexts such as the European one (21–23) and demonstrated the cost-effectiveness of ESDM intervention (17, 18). Overall, the ESDM approach has been shown to significantly increase cognitive, communication and adaptive skills at the group level (24). However, the inter-individual variability in child response to treatment (RTT) is high, as with all types of EI (25). To date, research about RTT in ESDM remains sparse and most studies focusing on homogeneous and individualized therapy settings comprised limited sample size. Younger age at start has emerged as an important moderator of optimal outcome, probably due to higher brain plasticity (26, 27). Age left aside, there are no behavioral characteristics child that are recommended by any international guidelines as a reliable individual predictor of RTT in ESDM, despite many attempts to identify some (14, 28). For instance, Vivanti et al. (29) attempted to identify predictors of RTT in children receiving G-ESDM intervention. Their study showed that developmental gains after one year of treatment were best predicted by higher imitation skills, goal understanding, and more advanced skills in the functional use of objects at baseline. This study offered insight into how children with certain baseline competencies might progress faster in a G-ESDM setting. However, outcomes were assessed after only 1 year of intervention and baseline measures used in this study were based on original tasks (i.e., specially developed for this study and not available in the common practice), making its results poorly reproducible. In addition, its group setting makes its conclusion hardly generalizable to the canonical individualized setting of ESDM. Besides, some authors identified that lower cognitive level at baseline could be related to higher RTT, although this effect could be biased by a larger potential for gain in children with very low cognitive profile (30, 31). This brief review shows that various behavioral characteristics (e.g., global cognitive level or imitation skills) at baseline modulate the outcome of an ESDM intervention. Nevertheless, none of these parameters has reached the status of being a reliable predictor of individual response to ESDM intervention recommended by international guidelines yet (14). It is therefore currently not possible to know to which extent the ESDM intervention will be effective when advising it. Yet, the identification of characteristics that promote the response to a specific intervention could in the future be of great help to the clinical practice when referring a child to one EI or another. Similarly, new approaches or goals could also be implemented to promote the emergence of these predictors to create cascading effects on children's intervention response. Great interindividual heterogeneity in response to intervention has been identified as a major limitation to this quest (13). A promising way of dealing with this heterogeneity relies on moving from a whole-group approach to the identification of distinct subgroups exhibiting specific patterns of response to intervention (32).

In the present study, we aim to identify early children's behavioral characteristics that could serve as predictors of outcome after receiving a specific and homogeneous NDBI (here, I-ESDM). To do so, we explored the developmental trajectories of 55 preschoolers with ASD who completed 2 years of individualized and intensive (20 h per week) ESDM intervention available in Geneva, Switzerland. We used a longitudinal single group design without a control population, similar to previous studies in the field (25, 26, 29). Indeed, because of ethical as well as logistic considerations, a random referencing to either the ESDM intervention program or any other community treatment was not achievable. We first investigated if our sample's outcome data, in terms of cognition, symptom severity and adaptive functioning, reflected findings described in the ESDM literature. We then parsed the heterogeneity in our sample's outcome by using cluster analysis (CA) and cognitive scores as the main outcome measure. CA highlighted three different groups based on cognitive outcome. We further explored baseline differences as well as early rates of change between the three groups to identify potential predictors of 2 year treatment outcome.

## METHODS

## Participants

Our original sample included 61 participants who completed 2 years of ESDM intervention in Geneva, Switzerland. Five participants were not included in the analyses because of missing data regarding their developmental assessment at baseline and one participant because of missing data at the end of the intervention. Missing evaluations were all caused by logistical issues (e.g., evaluation material not available at this time) and not because of children characteristics (e.g., invalid evaluation because of the child's behavior). Full description of the six excluded children is provided in **Supplementary Table 3**. There was no significant difference between the excluded participants and the final sample. Our analyses were thus based on the data collected from 55 participants (see **Table 1**).

There was no exclusion criteria based on co-occurring somatic, neurologic, or genetic disorder, as long as they were not affecting the validity of behavioral measures (e.g., major cerebral palsy). There was no systematic genetic or neurological screening done in our protocol. Genetic, somatic and neurologic diagnosis were screened with parental questionnaires. To our knowledge, no children were affected by any neurologic condition (e.g., epilepsy) diagnosed by a neurologist following active consultation by parents. No parents reported any diagnosis of major somatic disorders that could have affected the validity of behavioral measures. Twenty-four participants' parents reported having met a clinical geneticist. Four of them reported a genetic finding that could be "causative for ASD" according to the geneticist's report.

All children were referred to the intervention program after receiving a clinical diagnosis of ASD according to Diagnostic and Statistical Manual of mental disorders, 5th edition (1) criteria and Autism Diagnosis Observation Schedule-Generic (ADOS-G) (33) or 2nd edition (ADOS-2) (34) diagnosis cut- offs. For children that were administered the ADOS-2 Toddler module (which does not provide a diagnostic cut-off) at baseline, the "mild to moderate concern for ASD" cut-off had to be overreached. All children assessed with a Toddler module at baseline met the diagnosis cut-off (using ADOS-2 module 1 or 2) on their visit 1 year later, even though this was not an inclusion criterion for our study.

Enrollment in the intervention program was also conditioned by an age criterion: participants had to be able to participate for two full years prior to age of school entry. In Geneva, a child has to be 4 years old by July 31st to enter school in August of the same year. In our sample, one child was too old (42 months old at baseline) to meet this criterion but was still enrolled in the program as there was an available position. This results in a sample that is fairly homogeneous in age at start (28.7 ± 5.1 months, see **Table 1**). At least one parent had to be fluent in either French or English. Therapists fluent in both these languages were available to provide intervention, follow-up and parental coaching. The latest census in Geneva (35) reports that 92.3% of the population use either French or English as a first language. We must add to this percentage the people fluent in French or English as a second language. Thus, the vast majority of the population in Geneva was eligible for the intervention program based on the language inclusion criterion. Besides, there has been increasing concerns about socio-economic representativeness of the samples used in EI research (36, 37). To date the majority of ESDM studies are based on a white population with high parental income and a college educated background (38). Geneva has a very culturally diverse population and the costs of the ESDM intervention program are almost completely covered (39). As a result, our sample is fairly representative of Geneva's residents socio-economic characteristics thus providing results with a very high degree of cultural and socio-economic generalizability compared to most studies in the field (see **Table 1**).

Ultimately, enrollment also depended on place availability at time of referral. The parents of all participants gave their written informed consent to the research protocol that was approved by the institutional review board of the University of Geneva. All participants were assessed in the context of the ongoing longitudinal Geneva Autism Cohort study. Twenty-two children from this same sample were already included in a previous study measuring outcome after 1 year of ESDM intervention
(40). Baseline evaluations were completed at the start of the intervention and comprised behavioral measures that are detailed below. Parents also filled out questionnaires regarding medical history, as well as demographic information detailed below. Children were then assessed at 3 other time points at 6, 12, and 24 months of therapy, for a total of 4 assessments. Post-intervention data about subsequent school placement and support needs were collected. Children went onto either regular educational classrooms with varied levels of in-class paraprofessional support or special education classrooms.

## Intervention

The 55 participants were enrolled in one of the 4 units of the *Centre d'Intervention Précoce en Autisme* (CIPA) in Geneva, Switzerland [Fondation Pôle Autisme (http://www.pole-autisme. ch) & Office Médico-Pédagogique], where they received 20 h a week of daily, individual intervention sessions using the Early Start Denver Model (ESDM). The ESDM is a comprehensive, evidence-based early intervention approach that promotes child learning through naturalistic developmental, and behavioral techniques (7, 41). Parents of the participants were provided with 12 h of once-a-week parent coaching sessions in the use of the ESDM model at the start of their child's program, and continued parent support sessions as needed throughout the 2-year period. The children were evaluated every 3 months using the Early Start Denver Model Curriculum Checklist for Young Children with Autism (ESDM-CC) to establish targeted and measurable learning objectives. The intervention services were provided by graduate-level therapists (at least Master's degree), who were trained within the CIPA program in the use of the ESDM approach, meeting ESDM fidelity on the ESDM Fidelity Rating System (41). Today, the team consists of 20 credentialed ESDM therapists, and the program is overseen by an ESDM certified trainer. Importantly, university background, ESDM training,

TABLE 1 | Sample characteristics over the 2 years of ESDM intervention.

| Measure | At Baseline | +6 months | +12 months | +24 months | Pval (R.M. ANOVA) | Partial eta squared | 0–24 mo | 0–12 mo | 12–24 mo |
|---|---|---|---|---|---|---|---|---|---|
| Clinical description | | | | | | | | | |
| ADOS CSS total [Mean (SD)] | 8.0 (1.9) | | 6.6 (2.0) | 6.6 (2.7) | <0.001*** | 0.169 | 0.002** | <0.001*** | 1.000 |
| ADOS CSS SA | 7.6 (2.0) | | 5.3 (1.7) | 5.5 (2.5) | <0.001*** (G) | 0.304 | <0.001*** | <0.001*** | 1.000 |
| ADOS CSS RRB | 8.0 (2.0) | | 9.1 (1.3) | 8.4 (2.7) | <0.007** (G) | 0.094 | 0.975 | <0.001*** | 0.122 |
| ADI-R subdomains [Mean (SD)] ($n = 51$) | | | | | | | | | |
| ADI-R social interactions | 14.2 (5.2) | | | | | | | | |
| ADI-R RRB | 4.0 (2.2) | | | | | | | | |
| VABS-II adaptive behavior composite [Mean (SD)] ($n = 48$) | 79.9 (9.4) | *81.3 (12.0)* | 80.7 (12.3) | 83.3 (16.1) | 0.046* (G) | 0.073 | 0.152 | 1.000 | 0.044* |
| VABS-II socialization | 80.6 (9.9) | *81.0 (9.9)* | 80.7 (10.2) | 80.4 (12.6) | 0.967 (G) | | | | |
| VABS-II communication | 75.6 (12.3) | *80.5 (14.8)* | 84.0 (17.7) | 87.6 (19.0) | <0.001*** (G) | 0.377 | <0.001*** | <0.001*** | 0.008** |
| VABS-II daily living skills | 83.57 (12.4) | *85.0 (11.6)* | 84.8 (11.8) | 84.5 (16.8) | 0.726 (G) | | | | |
| VABS-II motor skills | 89.5 (11.6) | *89.4 (11.0)* | 89.9 (10.6) | 90.1 (15.2) | 0.920 (G) | | | | |
| Composite DQ [Mean (SD)] | 60.1 (17.6) | *71.7 (20.9)* | 77.0 (25.0) | 80.0 (28.1) | <0.001*** | 0.325 | <0.001*** | <0.001*** | 1.000 |
| Fine motricity DQ | 74.3 (17.0) | *76.1 (16.0)* | 76.1 (18.4) | 81.7 (25.5) | 0.035 (G)* | 0.063 | 0.088 | 1.000 | 0.132 |
| Visual reception DQ | 74.6 (22.9) | *85.3 (23.5)* | 88.6 (30.8) | 88.6 (30.7) | <0.001*** (G) | 0.150 | 0.003 | <0.001*** | 1.000 |
| Expressive language DQ | 44.0 (19.2) | *56.8 (25.3)* | 66.4 (29.3) | 68.7 (28.0) | <0.001*** (G) | 0.447 | <0.001*** | <0.001*** | 0.782 |
| Receptive language DQ | 47.4 (26.2) | *68.8 (29.0)* | 76.8 (30.1) | 79.0 (33.6) | <0.001*** (G) | 0.432 | <0.001*** | <0.001*** | 1.000 |
| Demographics | | | | | | | | | |
| Chronological age [months Mean (SD)] | 28.7 (5.1) | | | | | | | | |
| Gender [females Number (percentage)] | 7 (12.7%) | | | | | | | | |
| Parental Education [Number (percentage)] ($n = 46$) | | | | | | | | | |
| Elementary school or high school | 21 (38.2%) | | | | | | | | |
| University or Ph.D. | 33 (60.0%) | | | | | | | | |
| Household income [Number (percentage)] ($n = 45$) | | | | | | | | | |
| <60 k | 14 (25.5%) | | | | | | | | |
| 60–140 k | 18 (32.7%) | | | | | | | | |
| >140 k | 21 (38.2%) | | | | | | | | |

*Scores at 6 months (in italic) are indicative and were not used in the repeated measure (R.M.) ANOVA. Scores with a significant difference are highlighted in bold; *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. G, Greenhouse-Geisser correction applied; ESDM, Early Start Denver Model.*

fidelity rating assessment and supervision by certified trainer does not differ across the four units. The separation in four units is essentially administrative and therapists are all part of the same team sharing the same supervisors, applying identical practice.

## Measures

The ADOS (which refers to the ADOS-G and its later version, the ADOS-2), is a standardized assessment which comprises a series of semi-structured social presses aimed to elicit and measure ASD symptoms (33, 34). The schedule comprises 5 different modules, adapted to the person's age and level of language. The calibrated severity score (CSS) was used to compare the total severity score as well as the restricted and repetitive behaviors (RRB) and social affect (SA) symptoms severity scores (42, 43). The ADOS were administered by a trained examiner and filmed. The members of the team who rated the video recordings were not implicated in the delivery of the ESDM intervention.

The Mullen Scales of Early Learning (MSEL) is a standardized assessment for children aged from birth to 68 months (44). It measures the child's development in five developmental domains: expressive language (EL), receptive language (RL), living skills (DLS) and motor skills. visual reception (VR), fine motor (FM), as well as gross motor skills (GM).The Psychoeducational Profile—third edition (PEP-3) is a standardized assessment tool that evaluates cognitive, motor, and adaptive domains in children 2–7 years of age (45). These domains include EL, RL, FM and cognitive verbal and preverbal (CVP). The PEP-3 as well as the MSEL were administered by psychologists following the standard instructions of both evaluations.

Developmental quotient scores (DQ) were computed for each subdomain of the MSEL by dividing the individual developmental age by the chronological age and multiplying by 100 as described in 2006 by Lord et al. (46). The composite DQ was computed by calculating the average of all four subdomains' developmental ages, then dividing by the chronological age and multiplying by 100. Similarly, DQ scores were computed for the subdomains of the PEP-3 that assess domains equivalent to those of the MSEL, namely EL, RL, CVP, and FM. The PEP-3 composite DQ was derived using the same formula as described for the MSEL, and has already been used for the PEP-3 subdomains in previous studies (40). For our analyses of cognitive skills, we used the MSEL Early Learning Composite DQ. Since the MSEL was not administered for some participants ($n = 7$ at baseline, $n = 7$ after 6 months of therapy, $n = 3$ after 12 months of therapy, $n = 2$ after 24 months of therapy) we replaced the missing DQ scores by their equivalent DQ scores derived from the PEP-3. It is important to keep in mind that DQ is normalized for the age at the time of evaluation. Hence, a DQ that remains stable over time does not reflect stagnation but rather continued developmental progress. Also, a loss of DQ over time does not necessarily imply regression (a loss of skills) but rather slower skill acquisition, leading to a widening of the gap between the child's current abilities and what would be expected in typical development.

An overall adaptive behavior composite score (ABC) of all these 4 domains is computed.

The ADOS, VABS-II, PEP-3 and MSEL were administered at baseline, after 12 months and after 24 months of therapy. Assessment at 6 months only comprised the VABS-II and the MSEL.

We measured participant socio-economic using the total household yearly income and the highest level of education achieved by parents at baseline. The household income was divided into three subgroups that are detailed in **Table 1**. Parental educational level was first coded using the seven categories of the four-factor index of social status developed by Hollingshead (48). We then divided these categories into two groups: (1) elementary school or high school completed, and (2) college and/or graduate degree completed.

## Rate of Change

For all behavioral measures acquired longitudinally (ADOS, VABS-II and DQ), we computed an individual rate of change using the following Symmetrized Percent Change (SPC) formula:

$$SPC\ \% = 100\ x \frac{(By - Bx)}{\{Bx + By)/2]}$$

Where $B_x$ and $B_y$ represent the behavioral measure acquired when the participant was aged of $age_x$ and $age_y$, respectively. In other words, SPC is the behavioral difference between two timepoints relatively to the mean of the scores across these two timepoints, then divided by the time interval (in years). This results in a yearly rate of change that can be expressed as a percentage when multiplied by 100. The main advantages of using symmetrized measures of change over absolute differences (such as $B_y - B_x$) or non-symmetrized percentages [such as $(B_y - B_x) / B_x$ ] comprise increased statistical robustness, higher reliability in small samples, limited sensitivity to outliers, and equivalent consideration of both $B_x$ and $B_y$ measures (49). Also, SPC was chosen over absolute difference because it is scaled for the global developmental level of the child. Analyzing the cognitive changes using absolute differences leads to considering a gain of 10 DQ points in a child with an initial DQ of 90 as equivalent to a gain of 10 points in a child with a 60 composite DQ at baseline. In contrast, using SPC would give more weight to the gains made by the child with the lower DQ at start despite the fact that the absolute change is identical. In children with ASD and low DQ, small absolute gains have a larger impact in their adaptive behavior compared to their peers with higher DQ (50). Hence, measuring rates of change relatively to each participant global developmental level as SPC appears more clinically meaningful.

## Statistical Analyses

SPSS Satistics v26.0.0.0 macOS (Armonk, NY: IBM Corp.) was used for all analyses. Statistical significance threshold was set at alpha = 0.05. Graphs were for obtained with Prism v8.3.0 and Matlab R2018b for MacOs (MathWorks). To test for an effect of time, a repeated measure ANOVA was performed on the whole sample for each longitudinal behavioral measure using the scores collected at baseline, 12 and 24 months after the start of the intervention services. Greenhouse-Geisser correction was applied whenever the assumption of sphericity was violated according to Mauchly test.

Until now, methodological strategies to identify intervention- specific predictors of EI outcome include whole-sample correlations between baseline and outcome measures (29, 51), comparison between subgroups defined based on an arbitrary cut-off such as rapid vs. slow learners (52) or best vs. non- best outcome (53, 54). A promising alternative relies on the identification of distinct phenotypic subgroups within ASD (32). Defining more homogeneous subgroups based on behavioral characteristics in a data-driven manner can be achieved by applying cluster analyses (CA), a strategy that has already been used in ASD preschool studies [for a review see (32)]. To date, CA has only been applied once on children with ASD participating in an EI program (Applied Behavioral Analysis: ABA) with a special focus on language development (55). We here performed a cluster analysis (CA) using cognition (assessed with the composite DQ measure) as our main outcome measure. There are several reasons why we chose DQ over other parameters. First, it is generally the main outcome measure reported in early intervention studies, and it displays the most variability (2, 56, 57). Second, cognition has been shown to be the domain that improves the most after early intervention (58). Third, studies investigating possible ASD subtypes within ASD have shown that the most salient group differences emerge when categorized by cognitive skills (59). We used a *k*-means clustering approach to identify subgroups in terms of DQ trajectories with a maximal number of iterations set to 10 (60). We chose two variables that capture individual DQ trajectories: the composite DQ at baseline and the composite DQ SPC over the 2-year intervention period. To objectively determine the number of clusters *k* we used a two-step clustering approach as suggested by Kodinariya and Makwana (61). We used the two-step clustering algorithm developed by Chiu et al. (62) as it is implemented in IBM® SPSS® Statistics. Briefly, this method firstly divides the sample into a set of sub-clusters through a sequential approach and secondly merges the sub-clusters through a hierarchical technique based on the log-likelihood distance between them. Finally, the Akaike's information criterion is used to objectively determine the optimal number of clusters.

The cluster analysis (CA) yielded 3 optimal clusters based on the baseline composite DQ and the composite DQ SPC over 2 years (**Figure 1**) with silhouette measure of cohesion and separation equal to 0.6. The ANOVA revealed that one of these clusters exhibited significantly greater composite DQ at baseline compared to the others and was therefore named "higher cognitive at baseline" (HC, $n = 20$). Its average DQ at baseline was 78.6 ± 10.9 with a range between 64.4 and 107.9 with a SPC of 9.9 ± 5.8 %/yr. This corresponds to an average 18.3 gain for a final DQ of 96.9 ± 14.3 with a range between 64.2 and 124.3. The second "optimal responders" cluster (OptR, $n = 24$) was characterized by high rates of progress within the 2-year program. DQ at baseline was 51.5 ± 10.7 with a range between 21.9 and 66.8, and its average SPC was 23.8 ± 7.9%/year. This corresponds to an average 34.6 gain for a final DQ of 86.2 ± 20.8 with a range between 32.5 and 130.3. The third "minimal responders" cluster (MinR, $n = 11$) was characterized by decreased rates of progress compared to the two other clusters with an average SPC of −11.5 ± 12.0%/yr. Its composite DQ at baseline was 44.9 ± 8.1 with a range between 31.7 and 59.1. The average loss was 9.1 for a final DQ of 35.8 ± 8.9 with a range between 24.5 and 58.0. The OptR and MinR subgroups did not differ in composite DQ at baseline, with an average of 51.5 and 44.9 respectively. Together, they form a group of children with lower cognitive scores (LC) at baseline. Cluster differences over composite DQ at baseline and composite DQ SPC are illustrated on **Figure 1**. Detailed analyses are reported in **Supplementary Tables 1, 2**.

Demographic, socio-economic measures and behavioral measures at baseline were compared between clusters using one- way analysis of variance (ANOVA) or chi-square test. We used a Bonferroni correction for multiple testing on the subdomains of the same clinical evaluation (e.g., the subdomains of the VABS-II), setting the statistical significance at 0.05/number of subdomains. When an ANOVA reached statistical significance, *post-hoc* comparisons between clusters were performed using multiple *T*-tests with Bonferroni correction and statistical significance set at 0.05/number of clusters.

We then applied the same strategy to compare the SPC between clusters. We performed analyses on the following SPC: from baseline to 6 months, from baseline to 12 months, from baseline to 24 months of therapy.

Finally, we focused on the two LC clusters which showed no differences in their composite DQ at baseline to explore whether any other behavioral measure could help classifying them. To do so, we used logistic regression models. More specifically, we selected all behavioral measures that differed between OptR and MinR on *post-hoc* *T*-tests at baseline. Then, we performed a multivariate logistic regression using the selected measures. Whenever a composite score and one or more subdomain scores of the same test were selected, we preferred the composite measure to minimize potential collinearity between variables in the model. Then, we used the same strategy for the SPC measures during the 6 first months of intervention, and ultimately with those of the 12 first months.

## Sample Size

Once the three clusters solution obtained, we were able to compute the estimated power to detect differences between groups. Based on a sample of 55 children divided in three clusters and assuming an alpha of 0.05 using ANOVA, we calculated 80% power to detect group differences of at least 0.430 effect size.

# RESULTS

## Whole Sample Trajectories

Descriptive measures collected at each visit are reported in **Table 1** for the total sample. The children were aged from 15.3 to 42.0 months at the beginning of the intervention (average: 28.7 ± 5.1 months). The average composite DQ of the entire group at baseline was 60.1 ± 17.6 (range: 21.9–107.9). As a group, all 55 children receiving ESDM showed a significant

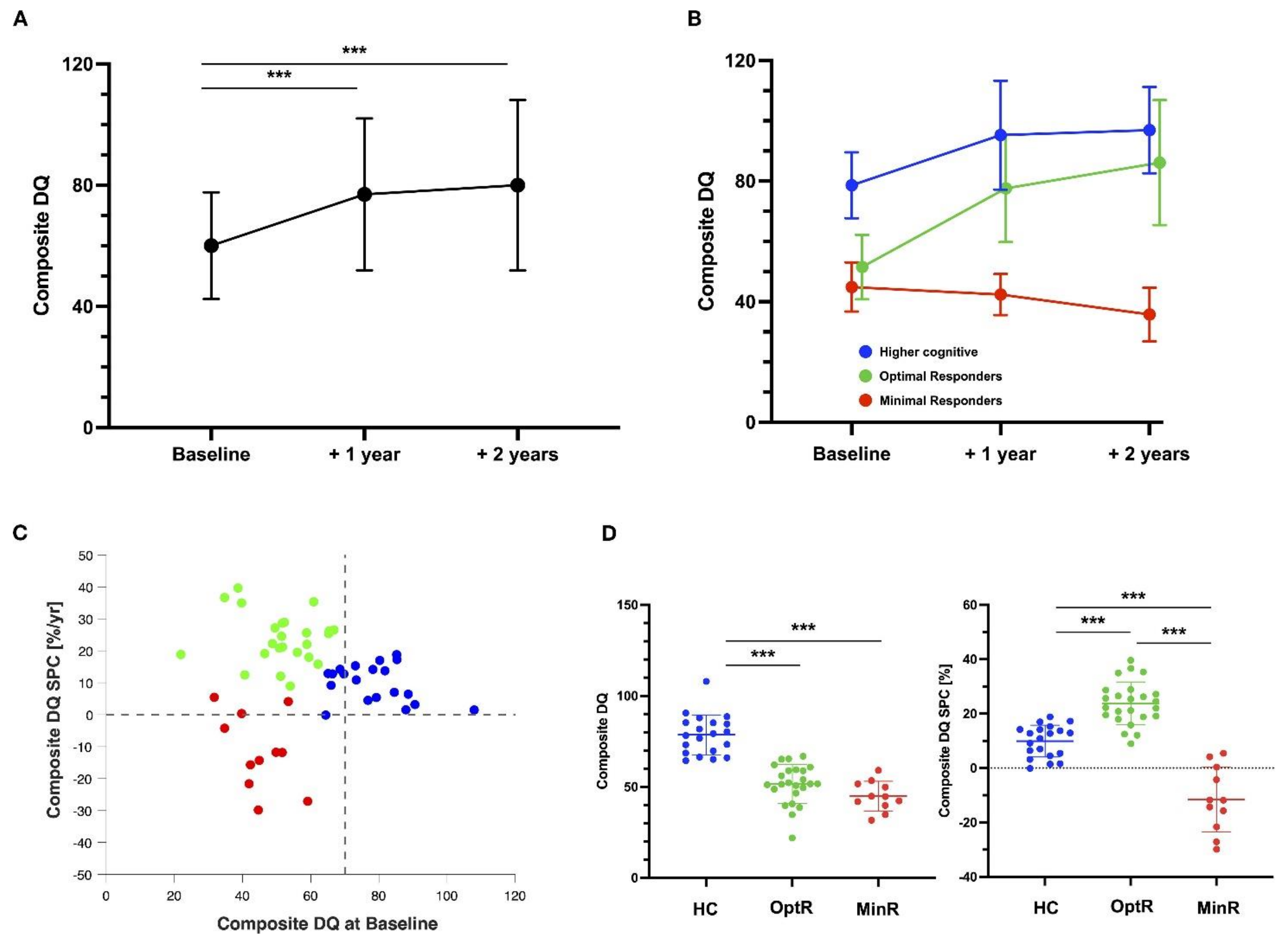


FIGURE 1 | (A) Composite DQ trajectory of the total sample over the 2 years of intervention. Significant results of repeated measure ANOVA are displayed. (B) Composite DQ trajectories of the three subgroups parsed by the cluster analysis. (C) Individual values of the two measures used in the clustering analysis algorithm (composite DQ at baseline and DQ SPC over the 2 years of interventions). Color code represents the cluster membership of each participant after the application of the cluster analysis. (D) Differences between the three subgroups on the two measures that were used to parse them. ***$p < 0.001$. DQ, Developmental quotient; HC, Higher cognitive; MinR, Minimal responders; OptR, Optimal responders; SPC, Symmetrized percent change.

decrease in their total level of symptom severity (ADOS CSS) (see **Table 1**). This improvement was driven by a decrease in the Social Affect (SA) domain. On the contrary, the RRB symptom severity increased over time. We found that these changes occurred mainly during the first year of intervention and that CSS (both RRB and SA) were stable during the second year of intervention. In parallel, participants' developmental scores improved. This improvement was significant in all subdomains (i.e., FM, VR, RL and EL). As for the measures of symptom severity, all changes in cognition were significant during the first year of therapy but not the second one, except for FM rates of change during first year that did not reach significance level in *post-hoc* analyses. Finally, increase in DQ was accompanied by an improvement of adaptive functioning as measured by the VABS ABC. This increase was significant during the second year of intervention only. More precisely, participants made significant gains in the communication subdomain which occurred both during the first and the second year of intervention. All statistically significant results are detailed in **Table 1**. Concerning the type of schooling after the intervention, 35 participants (63.6%) joined a public regular education classroom with individual educational support. One participant (1.8%) joined a regular education classroom without any support. Four children (7.3%) entered a private school that provided in-class support in a regular education classroom. Finally, 15 participants (27.3%) entered special education program within the public-school system.

## Parsing the Heterogeneity in Treatment Response

### Difference Between the Three Subgroups at Baseline

We found no differences between clusters for parental educational attainment or household income (see **Supplementary Table 1**). Inclusion procedure resulted in a sample that was relatively homogeneous in age at baseline (28.7 ± 5.1 months). Yet we compared age at baseline between groups to exclude this variable as a confound factor and found no difference regarding age at baseline. When looking at DQ at baseline, we found that HC showed higher scores in all DQ subdomains compared to both other clusters. Considering adaptive behavior, HC exhibited higher scores in ABC as well as in the communication subdomain compared to both other clusters. HC also showed a higher score in adaptive socialization and motor skills compared to MinR. All statistically significant results of analyses on the DQ and the VABS-II across the three subgroups at baseline are illustrated on **Figure 2**. There was no difference in the total ADOS CSS. In the ADOS subdomains, we found that HC exhibited lower RRB compared to MinR. Besides, the only difference between MinR and OptR was in global adaptive functioning (VABS ABC), MinR showing lower scores (70.7 ± 5.2) at baseline compared to OptR (78.5 ± 7.5).

## Differences Between Subgroups in Rates of Change Over 6, 12, and 24 Months of Intervention

We found that over the 2 years of therapy, OptR exhibited higher rates of change compared to the other two subgroups in cognition (composite DQ as well as VR, FM and RL subdomains). They also showed higher rates of change in adaptive behavior compared to MinR (VABS-II ABC, in socialization, communication, and DLS subdomains) (see **Supplementary Table 2**). These differences between MinR and OptR were already present within the 12 first months of therapy in the communication subdomain. Also, we found that MinR exhibited slower rates of change during the total time of intervention compared to both other subgroups in cognition (composite DQ, VR, FM and EL) as well as in adaptive behavior (VABS-II ABC, socialization, communication and DLS). Differences in the rates of change of composite DQ, VR and EL between MinR and OptR were already significant during the first year of intervention.

Finally, we found that OptR already exhibited faster rates of change in composite DQ, and adaptive functioning (VABS ABC) compared to MinR (**Figure 3**) after only 6 months of intervention. These differences in early DQ and VABS ABC rates of change were driven by RL and adaptive communication SPC.

We did not find any difference in the rates of change of symptom severity (total ADOS, SA and RRB) between the three subgroups during the time of intervention.

## Subgroup Classification Based on Early Rates of Change

Minimal responders (MinR) and optimal responders (OptR) showed no difference on the composite DQ at baseline and were both considered to have lower cognitive scores at baseline (LC). They were thus selected for our classification analyses to address the potential of clinical measures at baseline as well as their early rates of progress to classify them. At baseline, these two subgroups differed in VABS ABC. Logistic regression based on this parameter allowed an overall classification precision of 70.4% (5 out of the 11 MinR and 21 out of the 23 OptR were classified

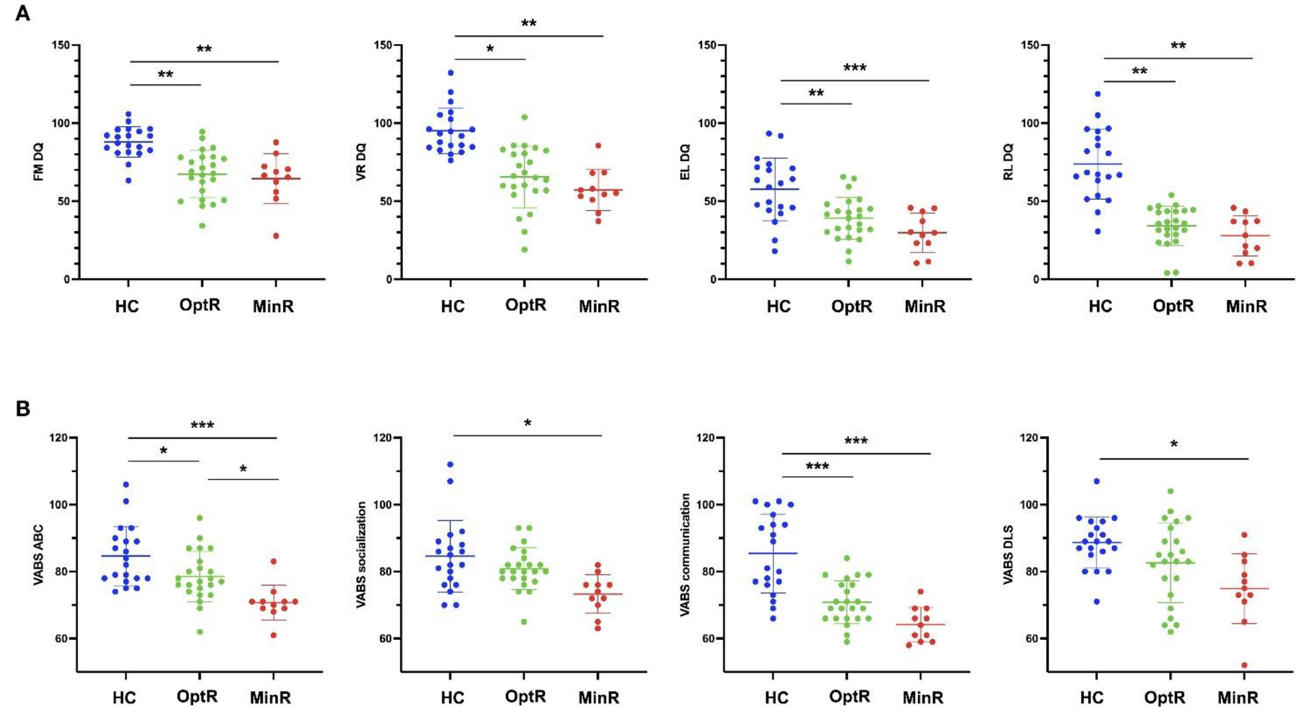


FIGURE 2 | (A) Statistically significant differences in DQ subdomains between subgroups at baseline. (B) Statistically significant differences in VABS-II ABC and VABS-II subdomains between subgroups at baseline. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. ABC, Adaptive behavior composite; DQ, Developmental quotient; EL, Expressive language; FM, Fine motor; HC, Higher cognitive; MinR, Minimal responders; OptR, Optimal responders; RL, Receptive language; VABS-II, Vineland adaptive behavior scale; VR, Visual reception.

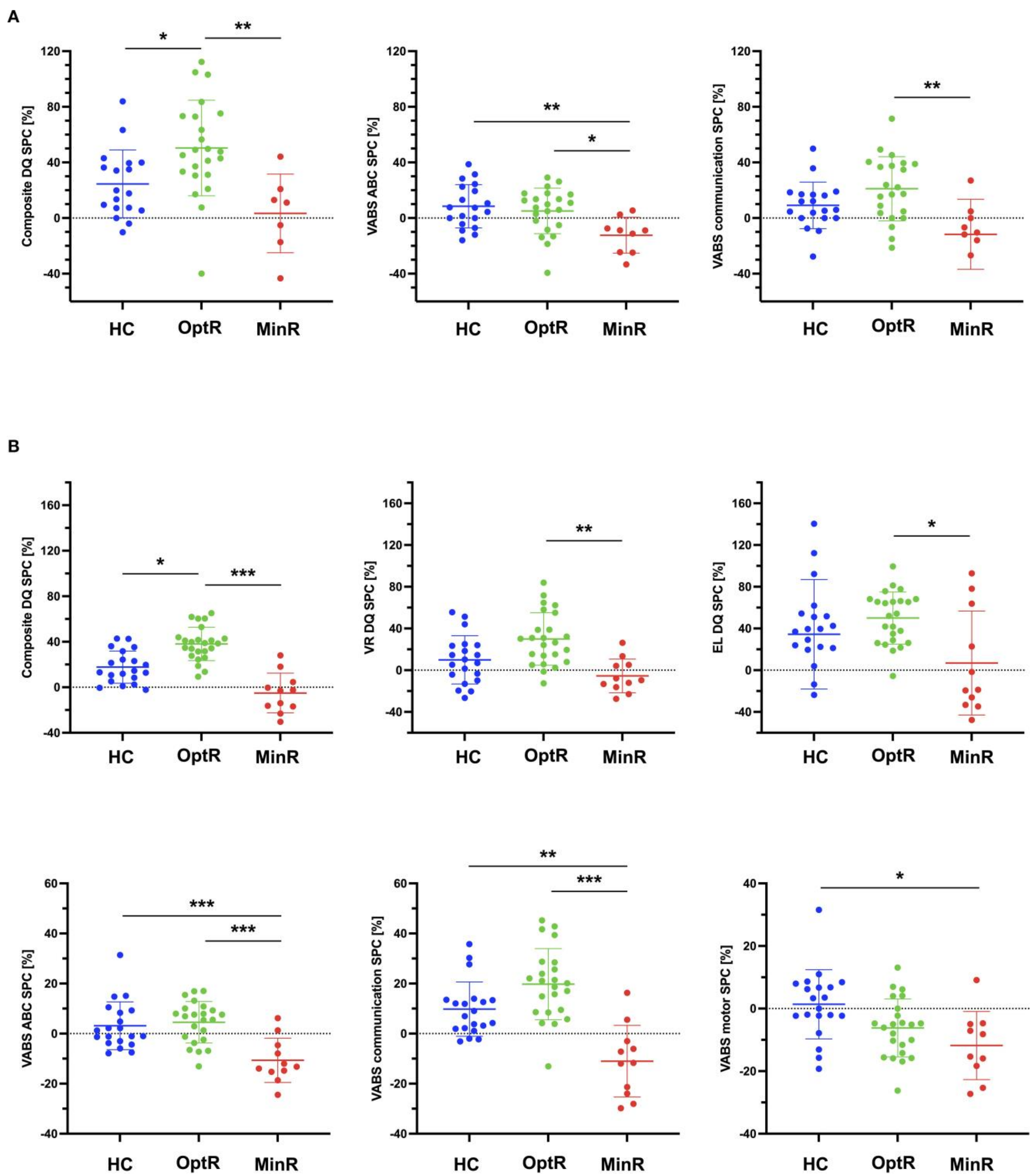


FIGURE 3 | (A) Statistically significant differences between subgroups in the rates of change of behavioral measures (DQ and VABS-II) within the first 6 months of intervention. (B) Statistically significant differences between subgroups in the rates of change of behavioral measures (DQ and VABS-II) within the first 12 months of intervention. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$. ABC, Adaptive behavior composite; DLS, Daily living skills; DQ, Developmental quotient; EL, Expressive language; FM, Fine motor; HC, Higher cognitive; MinR, Minimal responders; OptR, Optimal responders; RL, Receptive language; SPC, Symmetrized percent change; VABS-II, Vineland adaptive behavior scale; VR, Visual reception.

correctly). The model was significant ($\chi^2 = 10.0$, $p = 0.002$) and explained 35.5% of the variance (Nagelkerke $R^2$).

Within the first 6 months of therapy, MinR showed slower SPC in the VABS-II ABC and in the composite DQ. Logistic regression based on these two variables allowed a partition of MinR and OptR with a 85.2% overall correct classification rate. Nineteen out of the 21 OptR included in the model and 4 out of the 6 MinR included were classified correctly. The logistic regression model was statistically significant ($\chi^2 = 10.2$, $p = 0.006$) and explained 48.0% of the variance (Nagelkerke $R^2$). The prediction equation was the following: $0 = -0.040 * DQ\ SPC - 0.112\ VABS\text{-}II\ ABC\ SPC - 0.92$.

Within the first 12 months of therapy, OptR exhibited higher SPC in both the VABS-II ABC and the composite DQ. Logistic regression performed with both measures reached a 94.3% rate of overall correct classification between OptR and MinR. Twenty- two out of the 23 OptR included in the model and 9 out of the 11 MinR included were classified correctly. The logistic regression model was statistically significant ($\chi^2 = 22.5$, $p < 0.001$) and explained 67.5% of the variance (Nagelkerke $R^2$). The prediction equation was the following: $0 = -0.070 * DQ\ SPC - 0.167\ VABS\text{-}II\ ABC\ SPC - 0.020$.

Ultimately, we combined the information at baseline with the rates of change to see if the classification model was enhanced (**Figure 4**). Combining VABS ABC at baseline with VABS ABC and DQ SPC within the first 6 months we achieved a model with 96.3% overall precision. Five of the 6 MinR and all of the 21 OptR were classified correctly (Nagelkerke $R^2 = 70.2\%$; $\chi^2 = 16.6$, $p = 0.001$; $0 = -0.268 * VABS\text{-}II\ ABC - 0.049 * DQ\ SPC - 0.151 * VABS\text{-}II\ ABC\ SPC + 19.450$). Combining VABS ABC at baseline with VABS ABC and DQ SPC within 12 months the model reached 94.1% overall precision. Ten of the 11 MinR and 22 of the 23 OptR were classified correctly (Nagelkerke $R^2 = 75.5\%$; $\chi^2 = 26.4$, $p < 0.001$; $0 = -0.188 * VABS\text{-}II\ ABC - 0.040 * DQ\ SPC - 0.191 * VABS\text{-}II\ ABC\ SPC + 13.107$).

In other words, it would have already been possible for a clinician to classify a child as being an OptR or MinR with 96.3% of accuracy after 6 months of intervention based on the child's adaptive functioning at baseline and its rates of change in adaptive functioning and cognition.

## DISCUSSION

In the present study, we analyzed data from one of the largest samples of children who underwent 2 years of intensive (20 h per week) and individualized ESDM intervention to identify predictors of their developmental outcome. Overall, we observed that preschoolers in our sample made significant cognitive progress and adaptive skill gains over the 2 years of intervention (see **Figure 1A**). Improvements in the current sample allowed 72.7% of the children to enter a regular education classroom post-intervention, which in Geneva requires the child to have near peer-level functioning. These results are consistent with those reported in other studies on ESDM-based intervention (2, 63). More specifically, our sample exhibited an average change in DQ (+19.9 points) that is very close to the one described in the randomized controlled trial (RCT) study by Dawson et al. (2), which reported 18 points of cognitive gain, an average significantly greater than that of their control group. In parallel, a naturalistic study that explored developmental trajectories in preschoolers with ASD who were not enrolled in any specific therapeutic program reported an average DQ gain of only 6.3 points between 24 and 48 months of age (64). The average initial DQ in the cited study (63.6 ± 11.5) was similar to ours (60.3 ± 18.0). Considering similarities in the outcome between our results and previous ESDM studies as well as differences with naturalistic studies, one can infer that ESDM intervention in our study had a causal effect on the improvements observed at the whole group level. These results therefore highlight the possibility of implementing ESDM in Europe as effectively as

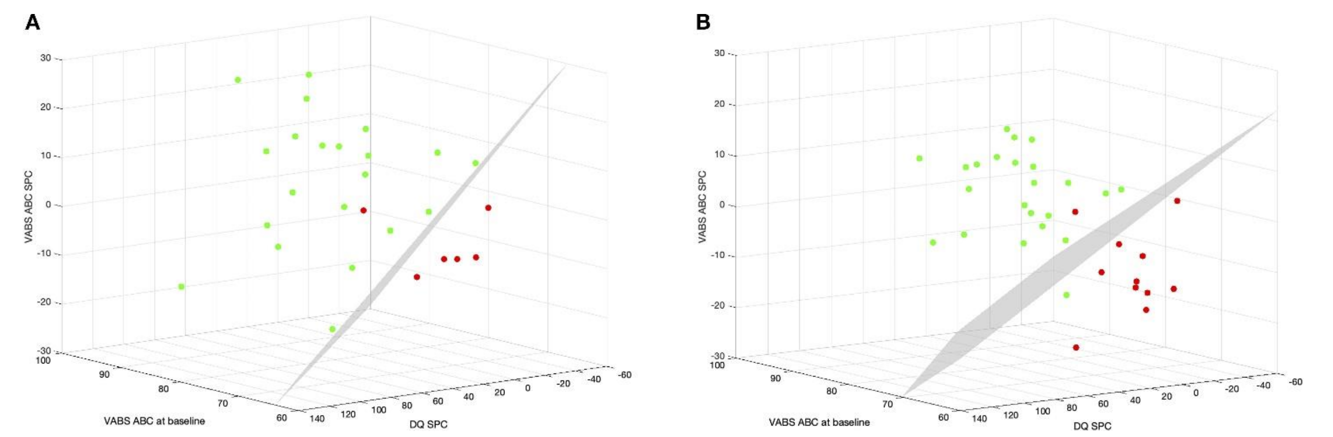


FIGURE 4 | (A) Multinomial logistic regression between MinR and OptR using their rates of change within the 6 first months of intervention in Composite DQ and VABS-II ABC, as well as their VABS-II ABC at baseline. Color code corresponds to subgroup membership (red: MinR, green: OptR). Decision boundary is represented in a dotted line. (B) Multinomial logistic regression between MinR and OptR using their rates of change within the 12 first months of intervention in Composite DQ and VABS ABC, as well as their VABS-II ABC at baseline. ABC, Adaptive behavior composite; DQ, developmental quotient; SPC, Symmetrized percent change; VABS-II, Vineland adaptive behavior scale.

in the US, despite differences in culture and health care system. They also support the cost-effectiveness of ESDM intervention, with improvements in cognition and adaptive behavior known to reduce subsequent school-based support needs, offsetting costs associated with early intensive intervention (17–19).

This study also aimed to determine whether preschoolers with ASD who participated in a 2-year NDBI intervention program (here ESDM in an individual setting, or I-ESDM) could be separated into distinct subgroups based on their cognitive trajectories over time. To achieve this, we used a *k*-means cluster analysis (CA) approach with cognitive abilities at baseline and cognitive rates of change over time as variables. CA yielded three groups: 36.4% ($n = 20$) of children with a mild cognitive delay at baseline that displayed a globally good outcome (Higher cognitive at baseline: HC), and two groups of children constituting the lower cognitive scores at baseline group (LC) that had very different outcomes. The first group of LC, which represented 43.6% ($n = 24$) of the entire sample, underwent significant cognitive and adaptive skill improvements (Optimal responders: OptR) while the second group of LC, which represented 20.0% ($n = 11$) of our sample, showed slower overall progress, and saw a widening of the developmental gap over time in cognition and adaptive behavior compared to same aged peers (Minimal responders: MinR). The clear distinction between toddlers with mild cognitive delay (HC) and those with the more severe cognitive delay at baseline (LC) observed in our sample is also reported in previous studies that applied CA to preschoolers with ASD (65–67). These studies identified at least two subgroups categorized as “high” and “low-functioning” based on early cross- sectional cognitive measures. One of the main differences in the present study is that we included a longitudinal variable in our CA (i.e., the rate of cognitive change) and were therefore able to further define our subgroups of LC children based on individual cognitive trajectories over time that a cross-sectional CA would have failed to capture. In our second analysis, we aimed to uncover potential predictors of outcome by evaluating how we can predict a child’s cluster membership. Amongst the LC subgroups (MinR and OptR), we found one difference at baseline in general adaptive functioning (see **Supplementary Table 1**). More importantly, we noted a significant difference between their rates of change in cognition and adaptive skills within the first 6 months of intervention. These differences were mostly driven by the progress in receptive language and adaptive communication. Using a logistic regression model, we showed that these early rates of change combined to differences at baseline predicted at 96.3% attrition to either the MinR or OptR subgroups. This means that higher adaptive functioning skills at baseline combined to early, rapid developmental progress by 6 months of intervention allowed an accurate classification of subsequent developmental pattern.

Our analyses of the HC subgroup suggest that a mild cognitive delay (78.6 ± 10.9 of composite DQ) at the start of an ESDM intervention is associated with an alleviation of the delay in cognitive skills (+9.9% DQ per year) and adaptive behavior (+4.2% ABC per year) over the course of treatment. In addition, children in the HC group exhibited higher levels of adaptive skills compared to other subgroups (84.9 ± 9.2 of ABC) at baseline, especially in the VABS-II domain of communication (84.7 ± 8.9). All HC children except for one were able to continue into a regular education classroom following the intervention. With a DQ of 64 at both the beginning and the end of the intervention, this child was the only one in the HC group with a DQ value lower than 80 at the end of the intervention. Overall, our HC subgroup results suggest a positive outcome (in terms of cognition, adaptive functioning and schooling) in preschoolers with a mild delay in cognition and communication at baseline after receiving an individualized and intensive ESDM intervention. A recent review concluded that a higher cognitive level at baseline is a good predictor of positive outcome after various types of EI (68). Also, previous studies focusing on another type of intervention (Applied Behavioral Analysis: ABA) reported that higher abilities in adaptive behavior (52, 69) as well as in language (70) constitute predictors of good outcome. This might suggest that mild delays in cognition and communication could represent a common predictor of good outcome among various EI approaches. These findings will need to be further explored with future RCT that assess the specific causality of ESDM intervention within these results. A practical implication of our findings concerning the HC subgroup is that clinicians who refer a toddler with a mild developmental delay at baseline to an ESDM program can be relatively confident that there will be a good outcome in cognition and adaptive behavior by the end of the intervention.

Apart from the HC group, the rest of the sample included children presenting a severe cognitive delay at baseline (Lower Cognitive, or LC). These children presented drastically different cognitive trajectories of change over time and were attributed to two distinct subgroups: OptR and MinR. Despite their severe cognitive delay at baseline (average DQ of 51.5 ± 10.7), the 24 children that composed the OptR subgroup greatly improved their cognitive and adaptive skills over time and 79.2% of them were able to join a regular education classroom with in-class support. On the other hand, the 11 children in the MinR subgroup had a similar level of cognitive impairment at baseline (average DQ of 44.9 ± 8.1), however their cognitive and adaptive functioning scores did not improve over time. Furthermore, the developmental gap between continued to widen, despite receiving intensive early intervention. Only 2 out of 11 (18.2%) MinR children joined a regular education classroom following the intervention. One clinical implication of our analyses of OptR and MinR at baseline is that the OptR constituted most of the LC children (68.6%) thus supporting the *a priori* that most toddlers who present with lower cognitive scores at intake display a positive outcome after receiving an individual intensive ESDM intervention. Nonetheless, a better understanding of the factors (behavioral, biological, and environmental) that are associated with MinR remains necessary to develop more targeted clinical recommendations. For instance, future studies including more participants with comorbid conditions such as epilepsy should investigate whether they represent moderator of outcome. Furthermore, they could determine whether the additive effect of various genetic mutations may moderate the outcome (71). In our sample, four participants had a reported genetic finding with a potential causal effect in ASD. Two of them were in the MinR group one in OptR and one in HC. Yet, the sample is far too small to draw any conclusion on the matter and future studies should address how genetic alterations modulate the RTT. The observation of two distinct trajectories of change in children with larger cognitive impairments at baseline could shed new light on the inconsistencies that exist between various studies that measured cognitive response to EI within LC preschoolers with ASD. For instance, one previous study concluded that children with this kind of profile only improve in fine motor skills and receptive language but not in adaptive behavior after receiving an early and intensive ABA intervention (72). Other studies focusing on ESDM reported an association between lower cognitive level at baseline and high cognitive gains (30, 31). One can hypothesize that the inter-individual heterogeneity of outcome reported by previous studies (30, 31, 72), as well as the differences in their results were potentially due to the existence of two latent subgroups (MinR and OptR) that may have driven results in opposite directions. Our results thus advocate for a more systematic subgroup phenotyping, including longitudinal variables, in future studies focusing on the clinical outcome of EI to better describe the phenotypic heterogeneity within LC preschoolers with ASD.

Finally, our results suggest that the outcome after 2 years of intervention for children with LC at baseline can be predicted by the end of the six first months of intervention with high accuracy. Adaptive functioning was the only clinical parameter that could help distinguish OptR from MinR at baseline, allowing an overall classification precision of 70.4%. Nonetheless, based on this single variable only 45.5% of MinR could be classified correctly resulting in a relatively poor sensitivity in MinR identification at baseline. Sensitivity to OptR was largely higher with 91.3% of them correctly classified at baseline. Thus, the clinical interest for using the VABS-II alone at baseline to discriminate between LC (OptR and MinR) appears very limited. Nonetheless, the OptR group's rates of change appear to be significantly higher than those observed in the MinR group within the first year for cognitive and adaptive skills (especially in communication). Our results are in line with those of Sallows and Graupner (52), who reported cognitive gain during the first year of an early and intensive ABA intervention as one of the best predictor of outcome at the end of the intervention. Furthermore, we found that based on adaptive functioning at baseline combined to the rates of change in cognition and adaptive functioning within the first 6 months of intervention, we could infer the outcome after 2 years of intervention. Together, these conclusions might shed light on the timing of RTT, and when children can be considered as "*non-responders*" as raised by Vivanti et al. (13). Indeed, our analyses suggest that the first 6 months to a year of intervention offers critical information about how a child will respond to ESDM intervention over time, and leads us to question whether an early, clear response to intervention can predict an optimal response overall. The emphasis on this early response to intervention as a predictor of long-term outcome has several clinical implications. One of them would be the importance of implementing regular, standardized follow-ups to measure children's cognition and adaptive behavior in the first 6 and 12 months, in addition to the systematic ESDM *Curriculum Checklist* (ESDM-CC) that is currently used in the model. An alternative could lie in the development of a standardized way to use the ESDM-CC to track the rate of developmental change and ultimately the post-intervention outcome. This type of early standardized follow-up could potentially alert the clinician of difficulties a MinR child might face. This does not mean that MinR should be given less resources in terms of intervention. Our results show that despite a less optimal response compared to others, MinR show improvements in their raw scores. In the perspective of personalized medicine, future studies should determine what is the best intervention for these children. It might be possible that they would benefit from earlier or longer or more intensive intervention. It could also be that another type of EI (other than ESDM) would provide them a more optimal outcome. More research is needed to understand what supports or program enhancements would allow a child with a slower response to intervention to have a more optimal outcome.

In summary, our results show that despite the lack of individual reliable predictors of outcome for children with ASD who present severe cognitive delays at baseline, the consideration of their early dynamic behavioral parameters may help predict their overall response to intervention. Further RCTs that explore the trajectories of subgroups similar to ours are needed to determine the precise effect of the ESDM on children with MinR and OptR profiles. More specifically, we need to understand whether ESDM helps OptR improve their outcome or if it prevents MinR from falling even further behind developmentally, or both. Another hypothesis to be addressed is whether ESDM has an influence in the relative number of participants that are affected to each subgroup—i.e., whether some OptR participants would have been MinR if they had not undergone an ESDM based therapy. Future research on the specific effects of ESDM on each subgroup could result in improved therapeutic guidelines that are more tailored to each child's individual developmental trajectory. Our study provides relevant variables that should be explored by future research at the beginning and during the very first months of an ESDM intervention.

## LIMITATIONS

Despite being one of the largest samples of preschoolers who benefited from a 2-year intensive and individualized ESDM program, the sample size of the present study limits the number as well as the size of subgroups that can be detected by a cluster analysis. Nevertheless, we took care to respect the commonly accepted prerequisites of cluster analyses, including the minimum sample size in each group or the number of factors in the analyses given the overall sample size (73, 74). It is possible that studies performed on larger samples could achieve more fine-grained subgrouping on a similar population based on the same measures and could lead to bigger subgroups, in turn increasing the statistical power to detect differences at baseline between lower cognitive clusters that we could not highlight.

Another limitation that is a direct consequence of the previous one lies in the choice of the main outcome. We chose parameters related to cognitive skills as the main clustering factors. However, it would have been possible to use other measures such as level of ASD symptoms, adaptive skills or even a combination of these two. The inclusion of more variables in the model could help in defining a larger number of clusters and therefore increase our understanding of the heterogeneity of ASD in a refined manner. However, this was not possible in the present study, because of the limited sample size. The addition of more variables in the model and the multiplication of clusters would have violated the cluster analysis assumptions, making its interpretation invalid. Studies with larger samples should include more clinical parameters and could also use outcome variables suggested by parents (75).

Within our sample, 7 children did not have their DQ at baseline assessed with the same test as the rest of the sample. Indeed, these 7 children were tested with the PEP-3 while the others were tested using the MSEL. Although the scores obtained *via* these two assessments show a strong consistency within our sample (Cronbach $\alpha = 0.914$, $n = 44$), it is not possible to affirm that they are equivalent due to their different design. Yet, the clustering analysis applied on the sample with the 7 children excluded yielded the same cluster solution. Nonetheless, this divergence in the test used for a minority of our children should be kept in mind when interpreting the results.

A last limitation here lies in a lack of a lower cognitive (LC) who did not undergo an ESDM intervention making difficult to evaluate the causality of ESDM intervention in the observed outcome of this specific population. Nevertheless, Hedval et al. reported that 87.7% of the preschoolers with ASD and LC at baseline (<70 of DQ) still had a DQ lower than 70 when assessed after 2 years without receiving any EI (76). Moreover, their delay in adaptive functioning worsened in all the VABS-II subdomains except for communication at the group level. In contrast, in the present study LC children with similar developmental pattern (MinR) only constituted 31.4% of our LC group, while the other LC participants (OptR) exhibited large improvements in DQ as well as in adaptive behaviors. Considering these results, one can infer a causal effect of ESDM in the progress made by children with important cognitive delay at start. The specific effects of ESDM compared to other types of EI still needs to be addressed with future RCT.

## CONCLUSION

In this study, we applied a cluster analysis to the largest European sample of preschoolers with ASD who participated in an ESDM program for 20 h a week over a 2-year period. Overall, we found that ASD symptom severity decreased, and cognitive delay improved over the intervention period. Furthermore, the cluster analysis suggested three main patterns of cognitive trajectories over time. First, children who displayed mild cognitive and adaptive behavioral delays at baseline tended to have a good developmental prognosis, finishing their 2 years of early intervention with cognitive and adaptive behavior scores within the normal range. Second, children who presented with severe cognitive delays at the start of their early intervention exhibited two dramatically different patterns of developmental trajectories. About a third of these children continued to fall behind developmentally, despite intensive therapy services. The two remaining thirds of the children, who presented with lower cognitive and adaptive behavior scores at the beginning of treatment, exhibited early and important gains in cognition and adaptive behavior which continued for the duration of the 2 years of intervention. We found that the two lower cognitive subgroups differed in their global adaptive functioning at baseline, although this parameter alone shows a limited sensitivity in identifying the children who will show slower gains. Nevertheless, our results suggest that it may be possible to predict, after only 6 months of early intervention, and with very high levels of accuracy, whether a child will have an overall minimal or optimal response to treatment, based on their early gains in cognition and adaptive behavior combined to their adaptive functioning at baseline. These results advocate for close monitoring using standardized cognitive and adaptive behavioral testing during the first 6 months of intervention, especially for children that exhibit a clinically significant cognitive delay at baseline. Having an understanding early-on of how a child is responding to early intervention could alert clinicians and parents to the need to adapt and enhance the child's treatment plan. Future studies are needed to replicate these findings, and to evaluate the kinds of treatment adaptations that would optimize child outcome for each ASD subgroup. Also, there is a need for longitudinal studies that provide a long-term follow-up in the years following the end of early intervention, to be able to assess whether the patterns of cognitive profiles and response to treatment observed remain stable over time. Overall, our results advocate for a more systematic use of subgroup phenotyping that includes longitudinal parameters when assessing the efficacy of an early intensive intervention, to better decipher the great heterogeneity of behavioral dynamics in treatment response.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, on a reasonable request.

## ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Swissethics—Commission d'éthique Suisse relative à la recherche sur l'être humain. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

## AUTHOR CONTRIBUTIONS

MS conceived and designed the study. MF, MG, NK, and FR participated in the data acquisition. MG and FR prepared and analyzed the data under the supervision of MS. MG and FR wrote the manuscript with the inputs from all other authors. All authors participated in interpretation of results and read and approved the final manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2022.835580/full#supplementary-material

## REFERENCES

1. American Psychiatric Association, editor. *Diagnostic and Statistical Manual of Mental Disorders: DSM-5*. 5th edition. Washington, DC: American Psychiatric Association (2013). doi: 10.1176/appi.books.9780890425596
2. Dawson G, Rogers SJ, Munson J, Smith M, Winter J, Greenson J, et al. Randomized, controlled trial of an intervention for toddlers with autism: the early start denver model. *Pediatrics.* (2010) 125:e17–23. doi: 10.1542/peds.2009-0958
3. Freitag CM, Feineis-Matthews S, Valerian J, Teufel K, Wilker C. The frankfurt early intervention program FFIP for preschool aged children with autism spectrum disorder: a pilot study. *J Neural Transm.* (2012) 119:1011–21. doi: 10.1007/s00702-012-0792-0
4. Koegel LK, Koegel RL, Harrower JK, Carter CM. Pivotal Response intervention I: overview of approach. *Res Pract Pers Sev Disabil.* (1999) 24:174–85. doi: 10.2511/rpsd.24.3.174
5. Lovaas OI, Schreibman L, Koegel RL. A behavior modification approach to the treatment of autistic children. *J Autism Child Schizophr.* (1974) 4:111–29. doi: 10.1007/BF02105365
6. Prizant BM, Wetherby AM, Rubin E, Laurent AC, Rydell P. *The Scerts Model: A Comprehensive Educational Approach for Children With Autism Spectrum Disorders*. Baltimore, MD: Brookes Publishing Co (2006).
7. Schreibman L, Dawson G, Stahmer AC, Landa R, Rogers SJ, McGee GG, et al. Naturalistic developmental behavioral interventions: empirically validated treatments for autism spectrum disorder. *J Autism Dev Disord.* (2015) 45:2411–28. doi: 10.1007/s10803-015-2407-8
8. Corsello CM. Early intervention in autism. *Infants Young Child.* (2005) 18:74–85. doi: 10.1097/00001163-200504000-00002
9. Eldevik S, Hastings RP, Hughes JC, Jahr E, Eikeseth S, Cross S. Meta-Analysis of early intensive behavioral intervention for children with autism. *J Clin Child Adolesc Psychol.* (2009) 38:439–50. doi: 10.1080/15374410902851739
10. Fuller EA, Kaiser AP. The effects of early intervention on social communication outcomes for children with autism spectrum disorder: a meta-analysis. *J Autism Dev Disord.* (2020) 50:1683–700. doi: 10.1007/s10803-019-03927-z
11. Howlin P, Magiati I, Charman T. Systematic review of early intensive behavioral interventions for children with autism. *Am J Intellect Dev Disabil.* (2009) 114:23–41. doi: 10.1352/2009.114:23-41
12. Warren Z, McPheeters ML, Sathe N, Foss-Feig JH, Glasser A, Veenstra-VanderWeele J. A systematic review of early intensive intervention for autism spectrum disorders. *Pediatrics.* (2011) 127:e1303–11. doi: 10.1542/peds.2011-0426
13. Vivanti G, Prior M, Williams K, Dissanayake C. Predictors of outcomes in autism early intervention: why don't we know more? *Front Pediatr.* (2014) 2:58. doi: 10.3389/fped.2014.00058
14. Fuentes J, Hervás A, Howlin P, ESCAP ASD Working Party. ESCAP practice guidance for autism: a summary of evidence-based recommendations for diagnosis and treatment. *Euro Child Adolesc Psychiatry.* (2021) 30:961–84. doi: 10.1007/s00787-020-01587-4
15. Zwaigenbaum L, Bauman ML, Choueiri R, Kasari C, Carter A, Granpeesheh D, et al. Early intervention for children with autism spectrum disorder under 3 years of age: recommendations for practice and research. *Pediatrics.* (2015) 136 (Suppl. 1):S60–81. doi: 10.1542/peds.2014-3667E
16. König IR, Fuchs O, Hansen G, Mutius E, von, Kopp MV. What is precision medicine? *Euro Respir J.* (2017) 50:1700391. doi: 10.1183/13993003.00391-2017
17. Cidav Z, Munson J, Estes A, Dawson G, Rogers SJ, Mandell D. Cost offset associated with early start denver model for children with autism. *J Am Acad Child Adolesc Psychiatry.* (2017) 56:777–83. doi: 10.1016/j.jaac.2017.06.007
18. Penner M, Rayar M, Bashir N, Roberts SW, Hancock-Howard RL, Coyte PC. Cost-Effectiveness analysis comparing pre-diagnosis autism spectrum disorder (ASD)-targeted intervention with Ontario's autism intervention program. *J Autism Dev Disord.* (2015) 45:2833–47. doi: 10.1007/s10803-015-2447-0
19. Peters-Scheffer N, Didden R, Korzilius H, Matson J. Cost comparison of early intensive behavioral intervention and treatment as usual for children with autism spectrum disorder in the Netherlands. *Res Dev Disabil.* (2012) 33:1763–72. doi: 10.1016/j.ridd.2012.04.006
20. Vivanti G, Stahmer AC. Can the early start denver model be considered ABA practice? *Behav Anal Pract.* (2021) 14:230–9. doi: 10.1007/s40617-020-00474-3
21. Colombi C, Narzisi A, Ruta L, Cigala V, Gagliano A, Pioggia G, et al. Implementation of the early start denver model in an Italian community. *Autism.* (2018) 22:126–33. doi: 10.1177/1362361316665792
22. Geoffray MM, Denis A, Mengarelli F, Peter C, Gallifet N, Beaujeard V, et al. Using ESDM 12 hours per week in children with autism spectrum disorder: feasibility and results of an observational study. *Psychiatr Danub.* (2019) 3:333–9. doi: 10.24869/psyd.2019.333
23. Devescovi R, Colonna V, Dissegna A, Bresciani G, Carrozzi M, Colombi C. Feasibility and outcomes of the early start denver model delivered within the public health system of the friuli venezia giulia Italian Region. *Brain Sci.* (2021) 11:1191. doi: 10.3390/brainsci11091191
24. Fuller EA, Oliver K, Vejnoska SF, Rogers SJ. The effects of the early start denver model for children with autism spectrum disorder: a meta-analysis. *Brain Sci.* (2020) 10:368. doi: 10.3390/brainsci10060368
25. Contaldo A, Colombi C, Pierotti C, Masoni P, Muratori F. Outcomes and moderators of early start denver model intervention in young children with autism spectrum disorder delivered in a mixed individual and group setting. *Autism.* (2020) 24:718–729. doi: 10.1177/136236131 9888344
26. Lombardo MV, Busuoli EM, Schreibman L, Stahmer AC, Pramparo T, Landi I, et al. Pre-treatment clinical and gene expression patterns predict developmental change in early intervention in autism. *Mol Psychiatry.* (2021) 26:7641–51. doi: 10.1038/s41380-021-01239-2

27. Webb SJ, Jones EJH, Kelly J, Dawson G. The motivation for very early intervention for infants at high risk for autism spectrum disorders. *Int J Speech Lang Pathol.* (2014) 16:36–42. doi: 10.3109/17549507.2013.861018
28. Lord C, Brugha TS, Charman T, Cusack J, Dumas G, Frazier T, et al. Autism spectrum disorder. *Nat Rev Dis Primers.* (2020) 6:5. doi: 10.1038/s41572-019-0138-4
29. Vivanti G, Dissanayake C, Zierhut C, Rogers SJ, Team VA. Brief report: predictors of outcomes in the early start denver model delivered in a group setting. *J Autism Dev Disord.* (2013) 43:1717–24. doi: 10.1007/s10803-012-1705-7
30. Devescovi R, Monasta L, Mancini A, Bin M, Vellante V, Carrozzi M, et al. Early diagnosis and early start denver model intervention in autism spectrum disorders delivered in an Italian public health system service. *Neuropsychiatr Dis Treat.* (2016) 12:1379–84. doi: 10.2147/NDT.S106850
31. Robain F, Franchini M, Kojovic N, Wood de Wilde H, Schaer M. Predictors of treatment outcome in preschoolers with autism spectrum disorder: an observational study in the greater Geneva area, Switzerland. *J Autism Dev Disord*. (2020) 50:3815–30. doi: 10.1007/s10803-020-04430-6
32. Ousley O, Cermak T. Autism spectrum disorder: defining dimensions and subgroups. *Curr Dev Disord Rep.* (2014) 1:20–8. doi: 10.1007/s40474-013-0003-1
33. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, DiLavore PC, et al. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. *J Autism Dev Disord.* (2000) 30:205–23. doi: 10.1023/A:1005592401947
34. Lord C, Rutter M, DiLavore PC, Risi S, Gotham K, Bishop SL. *Autism Diagnostic Observation Schedule, 2nd edition (ADOS-2)*. Los Angeles, CA: Western Psychological Services (2012).
35. Office Fédéral de la Statistique/Office Cantonal de la Statistique. *Relevé Structurel: Population Résidante Selon L'origine et la ou les Langue(s) Principale(s) de 2015 à 2019* (2021). Available online at: https://www.ge.ch/ statistique/tel/domaines/01/01_06/T_01_06_1_01.xls
36. Mirenda P, Colozzo P, Smith V, Kroc E, Kalynchuk K, Rogers SJ, et al. A randomized, community-based feasibility trial of modified ESDM for toddlers with suspected autism. *J Autism Dev Disord*. (2022) 13:1–20. doi: 10.1007/s10803-021-05390-1
37. Nahmias AS, Pellecchia M, Stahmer AC, Mandell DS. Effectiveness of community-based early intervention for children with autism spectrum disorder: a meta-analysis. *J Child Psychol Psychiatry.* (2019) 60:1200–9. doi: 10.1111/jcpp.13073
38. Rogers SJ, Yoder P, Estes A, Warren Z, McEachin J, Munson J, et al. A multisite randomized controlled trial comparing the effects of intervention intensity and intervention style on outcomes for young children with autism. *J Am Acad Child Adolesc Psychiatry.* (2020) 60:710–22. doi: 10.1016/j.jaac.2020.06.013
39. Office Cantonal de la statistique. *Mémento Statistique du Canton de Genève*. Office Cantonal de la statistique (2017). Available online at: https://statistique. ge.ch/tel/publications/2017/donnees_generales/memento/dg-ms-2017.pdf
40. Franchini M, Zöller D, Gentaz E, Glaser B, Wood de Wilde H, Kojovic N, et al. Early adaptive functioning trajectories in preschoolers with autism spectrum disorders. *J Pediatr Psychol*. (2018) 43:800–13. doi: 10.1093/jpepsy/jsy024
41. Rogers SJ, Dawson G. *Early Start Denver Model for Young Children With Autism: Promoting Language, Learning, and Engagement*. New York, NY: Guilford Press (2010)
42. Gotham K, Pickles A, Lord C. Standardizing ADOS scores for a measure of severity in autism spectrum disorders. *J Autism Dev Disord.* (2009) 39:693–705. doi: 10.1007/s10803-008-0674-3
43. Hus V, Gotham K, Lord C. Standardizing ADOS domain scores: separating severity of social affect and restricted and repetitive behaviors. *J Autism Dev Disord.* (2014) 44:2400–12. doi: 10.1007/s10803-012-1719-1
44. Mullen EM. *Mullen Scales of Early Learning.* Circle Pines, MN: AGS (1995).
45. Schopler E, Lansing MD, Reichler RJ, Marcus LM. *Psychoeducational Profile: TEACCH Individualized Assessment for Children With Autism Spectrum Disorders.* 3rd edition. Austin, TX: Pro-Ed, Inc (2005). doi: 10.1037/t52601-000
46. Lord C, Risi S, DiLavore PS, Shulman C, Thurm A, Pickles A. Autism from 2 to 9 years of age. *Arch Gen Psychiatry.* (2006) 63:694–701. doi: 10.1001/archpsyc.63.6.694
47. Sparrow SS, Balla DA, Cicchetti DV. *Vineland II: Vineland Adaptive Behavior Scales*. American Guidance Service (2005). doi: 10.1037/t15164-000
48. Hollingshead AA. *Four-Factor Index of Social Status*. New Haven, CT: Yale University (1975).
49. Berry DA, Ayers GD. Symmetrized percent change for treatment comparisons. *Am Stat.* (2006) 60:27–31. doi: 10.1198/000313006X90684
50. Green SA, Carter AS. Predictors and course of daily living skills development in toddlers with autism spectrum disorders. *J Autism Dev Disord.* (2014) 44:256–63. doi: 10.1007/s10803-011-1275-0
51. Klintwall L, Eikeseth S. Number and controllability of reinforcers as predictors of individual outcome for children with autism receiving early and intensive behavioral intervention: a preliminary study. *Res Autism Spectr Disord.* (2012) 6:493–9. doi: 10.1016/j.rasd.2011.07.009
52. Sallows GO, Graupner TD. Intensive behavioral treatment for children with autism: four-year outcome and predictors. *Am J Ment Retard.* (2005) 110:417–38. doi: 10.1352/0895-8017(2005)110[417:IBTFCW]2.0.CO;2
53. Perry A, Cummings A, Geier J, Freeman N, Hughes S, LaRose L, et al. Effectiveness of intensive behavioral intervention in a large, community-based program. *Res Autism Spectr Disord.* (2008) 2:621–42. doi: 10.1016/j.rasd.2008.01.002
54. Sallows GO, Graupner TD. *Replicating Lovaas' Treatment and Findings: Preliminary Results 1*. In PEACH. London (1999).
55. Frazier TW, Klingemier EW, Anderson CJ, Gengoux GW, Youngstrom EA, Hardan AY. A longitudinal study of language trajectories and treatment outcomes of early intensive behavioral intervention for autism. *J Autism Dev Disord.* (2021) 51:4534–50. doi: 10.1007/s10803-021-04 900-5
56. Landa RJ. Efficacy of early interventions for infants and young children with, and at risk for, autism spectrum disorders. *Int Rev Psychiatry.* (2018) 30:25–39. doi: 10.1080/09540261.2018.1432574
57. Smith T, Groen AD, Wynn JW. Randomized trial of intensive early intervention for children with pervasive developmental disorder. *Am J Ment Retard* (2000) 105:269–85. doi: 10.1352/0895-8017(2000)105<0269:RTOIEI>2.0.CO;2
58. Rodgers M, Simmonds M, Marshall D, Hodgson R, Stewart LA, Rai D, et al. Intensive behavioural interventions based on applied behaviour analysis for young children with autism: an international collaborative individual participant data meta-analysis. *Autism.* (2021) 25:1137–53. doi: 10.1177/1362361320985680
59. Witwer AN, Lecavalier L. Examining the validity of autism spectrum disorder subtypes. *J Autism Dev Disord.* (2008) 38:1611–24. doi: 10.1007/s10803-008-0541-2
60. Hartigan JA, Wong MA. Algorithm AS 136: a K-Means clustering algorithm. *Appl Stat.* (1979) 28:100. doi: 10.2307/2346830
61. Kodinariya T, Makwana PR. *Review on Determining Number of Cluster in K-Means Clustering.* Undefined (2013). Available online at: /paper/Review-on-determining-number-of-Cluster-in-K-Means-Kodinariya-Makwana/1a34936bffe558a380168b790dc37956813514ba
62. Chiu T, Fang D, Chen J, Wang Y, Jeris C. A robust and scalable clustering algorithm for mixed type attributes in large database environment. In: *KDD '01, Proceedings of the Seventh QCM SIGKDD Internqtional Conference on Knowledge Discovery and Data Mining*. San Francisco, CA (2001). doi: 10.1145/502512. 502549
63. Rogers SJ, Estes A, Lord C, Vismara L, Winter J, Fitzpatrick A, et al. Effects of a brief early start denver model (ESDM)–based parent intervention on toddlers at risk for autism spectrum disorders: a randomized controlled trial. *J Am Acad Child Adolesc Psychiatry.* (2012) 51:1052–65. doi: 10.1016/j.jaac.2012.08.003
64. Clark MLE, Barbaro J, Dissanayake C. Continuity and change in cognition and autism severity from toddlerhood to school age. *J Autism Dev Disord.* (2017) 47:328–39. doi: 10.1007/s10803-016-2954-7
65. Fein D, Stevens M, Dunn M, Waterhouse L, Allen D, Rapin I, et al. Subtypes of pervasive developmental disorder: clinical characteristics. *Child Neuropsychol.* (1999) 5:1–23. doi: 10.1076/chin.5.1.1.7075
66. Stevens MC, Fein DA, Dunn M, Allen D, Waterhouse LH, Feinstein C, et al. Subgroups of children with autism by cluster analysis: a

longitudinal examination. *J Am Acad Child Adolesc Psychiatry.* (2000) 39:346–
52. doi: 10.1097/00004583-200003000-00017
67. Zheng S, Hume KA, Able H, Bishop SL, Boyd BA. Exploring developmental and behavioral heterogeneity among preschoolers with ASD: a cluster analysis on principal components. *Autism Research.* (2020) 13:796–809. doi: 10.1002/aur.2263
68. Zachor DA, Ben-Itzchak E. Variables affecting outcome of early intervention in autism spectrum disorder. *J Pediatr Neurol.* (2017) 15:129–33. doi: 10.1055/s-0037-1601444
69. Eldevik S, Hastings RP, Hughes JC, Jahr E, Eikeseth S, Cross S. Using participant data to extend the evidence base for intensive behavioral intervention for children with autism. *Am J Intellect Dev Disabil.* (2010) 115:381–405. doi: 10.1352/1944-7558-115.5.381
70. Magiati I, Moss J, Charman T, Howlin P. Patterns of change in children with autism spectrum disorders who received community based comprehensive interventions in their pre-school years: a seven year follow-up study. *Res Autism Spectr Disord.* (2011) 5:1016–27. doi: 10.1016/j.rasd.2010. 11.007
71. Warrier V, Zhang X, Reed P, Havdahl A, Moore TM, Cliquet F, et al. Genetic correlates of phenotypic heterogeneity in autism [Preprint]. *Genet Genomic Med*. (2020). doi: 10.1101/2020.07.21. 20159228. [Epub ahead of print].
72. Ben-Itzchak E, Watson LR, Zachor DA. Cognitive ability is associated with different outcome trajectories in autism spectrum disorders. *J Autism Dev Disord.* (2014) 44:2221–9. doi: 10.1007/s10803-014-2091-0
73. Formann AK. *Die Latent-Class-Analyse: Einführung in die Theorie und Anwendung [Latent class Analysis: Introduction to Theory and appLication*]. Weinheim: Beltz (1984)
74. Qiu W, Joe H. Generation of random clusters with specified degree of separation. *J Classif.* (2006) 23:315–34. doi: 10.1007/s00357-006-0018-y
75. McConachie H, Livingstone N, Morris C, Beresford B, Couteur AL, Gringras P, et al. Parents suggest which indicators of progress and outcomes should be measured in young children with autism spectrum disorder. *J Autism Dev Disord.* (2018) 48:1041–51. doi: 10.1007/s10803-017-3282-2
76. Hedvall Å, Westerlund J, Fernell E, Holm A, Gillberg C, Billstedt E. Autism and developmental profiles in preschoolers: stability and change over time. *Acta Paediatr.* (2014) 103:174–81. doi: 10.1111/apa.12455

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## 6.3 Full length article: Study 3

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RESEARCH ARTICLE Open

# The impact of social complexity on the visual exploration of others' actions in preschoolers with autism spectrum disorder

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**Abstract**

**Background:** Typical development of socio-communicative skills relies on keen observation of others. It thus follows that decreased social attention negatively impacts the subsequent development of socio-communicative abilities in children with autism spectrum disorders (ASD). In addition, studies indicate that social attention is modulated by context and that greater social difficulties are observed in more socially demanding situations. Our study aims to investigate the effect of social complexity on visual exploration of others' actions in preschoolers.

**Methods:** To investigate the impact of social complexity, we used an eye-tracking paradigm with 26 typically developing preschoolers (TD, age = 3.60 ± 1.55) and 37 preschoolers with ASD (age = 3.55 ± 1.21). Participants were shown videos of two children engaging in socially simple play (parallel) versus socially complex play (interactive). We subsequently quantified the time spent and fixation duration on faces, objects, bodies, as well as the background and the number of spontaneous gaze shifts between socially relevant areas of interest.

**Results:** In the ASD group, we observed decreased time spent on faces. Social complexity (interactive play) elicited changes in visual exploration patterns in both groups. From the parallel to the interactive condition, we observed a shift towards socially relevant parts of the scene, a decrease in fixation duration, as well as an increase in spontaneous gaze shifts between faces and objects though there were fewer in the ASD group.

**Limitations:** Our results need to be interpreted cautiously due to relatively small sample sizes and may be relevant to male preschoolers, given our male-only sample and reported phenotypic differences between males and females.

**Conclusion:** Our results suggest that similar to TD children, though to a lesser extent, visual exploration patterns in ASD are modulated by context. Children with ASD that were less sensitive to context modulation showed decreased socio-communicative skills or higher levels of symptoms. Our findings support using naturalistic designs to capture socio-communicative deficits in ASD.

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## Background

Autism spectrum disorder (ASD) is a group of pervasive neurodevelopmental disorders characterized by impairments in communication, social interactions and the presence of restricted and repetitive behaviors (DSM-5) [1]. A core symptom of ASD, often reported early on by parents, is a difficulty modulating eye contact. Based on this observation, studies have focused on the possible link between atypical visual exploration and social difficulties in autism using eye-tracking technology. The majority of these studies have shown decreased attention to social stimuli in individuals with ASD (often referred to as a lack of social orienting) and less time spent on the eye region compared to people with typical development [2–9] which were more evident when using dynamic (as opposed to static) stimuli [10] and naturalistic social interactions [2]. In addition, studies of high-risk children indicate that atypical social orienting emerges early in development, [8, 11–13] and shapes future developmental trajectories of children with ASD [5, 14, 15].

Decreased social attention among people with ASD compromises their ability to monitor others' actions early in development [16]. Monitoring others' actions is critical to social skills that emerge during infancy as watching others actions will give children the opportunity to learn from it and give them the opportunity to develop higher cognitive skills like joint attention, a core impairment in ASD (e.g. [17, 18]). Joint attention is, in turn, key to the subsequent development of other socio-communicative skills [19, 20], which will also support action monitoring by increasing the significance of gaze following, making it central to understanding the mechanisms underlying social development in ASD (for a review of the literature see [21]). Most studies investigating joint attention skills in ASD induce instances of joint attention to quantify the number of times participants accurately follow cues. While such study designs allow for the quantification of joint attention impairments at differential stages in ASD [22–24], they can be unrepresentative of daily life.

Unlike studies using controlled paradigms, Shic et al. [16] used a naturalistic eye-tracking task to track how toddlers monitor others' activity. They showed participants a video of an adult and a child solving a puzzle together. Twenty-month-old toddlers with ASD looked less at the shared activity and were more often distracted by the background compared to their typically developing (TD) peers. The authors concluded that this decreased monitoring of others' actions can be attributed to decreased joint attention skills in ASD children and *"a limited appreciation for the significance of the shared focus of others"* [16 pp. 5–6]. The use of such a task, one that is closer to everyday life, undoubtedly makes it possible to capture skills that are used in everyday life and to more accurately report the difficulties encountered on a daily basis by children with ASD. The task used by Shic et al. [16] therefore represents an ecologically valid design to investigate others' actions monitoring and sub- sequent joint attention behaviors in children with ASD. Shic et al. [16] however did not present different social context to investigate how visual exploration is modulated by social complexity.

Social context indeed appears to be a key determinant in divergent visual exploration between children with ASD and TD [25–28]. Studies indicate reduced attention to faces during dyadic bid [26, 28], tickles [28] and joint attention conditions [26],whereas individuals with ASD demonstrate TD-like visual exploration while watching someone make a sandwich [26], play peek-a-boo or sing a song [28]. To further refine diagnostic techniques and shape targeted interventions, it will be essential to further our understanding of the social contexts that accompany atypical visual exploration in ASD. In the current study, we investigate how children monitor others' actions during passive viewing, one of the primary building blocks of social learning during early development.

Harrop et al. [27] recently used a paradigm inspired from Chevallier et al. [2] that brings together dynamic stimuli with high ecological validity while manipulating context, or what they labelled « *social richness*». The authors presented videos of siblings practicing parallel play or interactive play to observe gender differences during social attention in ASD. In both conditions, males with ASD showed decreased attention to faces, whereas females with ASD demonstrated decreased attention during the interactive condition only and TD-like attention during the parallel condition, thereby reinforcing the idea of context-dependent attentional difficulty in ASD. While similar to Shic et al.'s [16] design, the aim of Harrop et al.'s study was to reveal gender differences during social attention. However, their design would be equally effective for investigating action monitoring and joint attention in children with ASD, due to the combination of ecological social interactions with differential social complexity. Parish-Morris et al. [29] recently reused this design with adults and showed that looking at interactive play compared to parallel play, increased attention to faces in both TD and ASD, though to a lesser extent in the ASD group. However, there are no studies focusing on preschoolers during the critical period for the development of socio-communicative skills. In addition, recent studies highlight the development of several compensatory mechanisms [30, 31] during the development of individuals with autism, making it difficult to assert that the skills observed in adulthood are the same as in childhood. Therefore, how children with ASD visually monitor others' actions and the way in which this exploration is modulated by social complexity remains unanswered and needs to be investigated considering that many socio-communicative skills emerge during infancy. In the present study, we aim to combine elements from those previous studies [16, 27, 29] to identify potential differences in the visual exploration of others' actions in preschoolers with ASD through the manipulation of context. Social complexity, or context, is manipulated in our design by showing videos of two children engaging in either parallel or interactive play. We then compare the time participants spent looking at different areas of the scene (faces, bodies, and objects) and the duration of their fixations, thought to reflect attentional engagement [32], by condition. To assess how participants dynamically view others' actions, we quantify the number of spontaneous gaze shifts between areas of interest (AOI). We hypothesize that children with ASD will exhibit decreased attention to faces in both conditions. However, based on previous results, we expect that the presence of an interaction will increase attention to socially relevant parts of the scene and make visual exploration more dynamic by reducing fixation duration and increasing the number of gaze shifts. Given that numerous studies have demonstrated strong correlations between symptom severity, level of adaptive behavior or cognitive skills and visual exploration patterns in children with ASD [13, 14, 16, 22, 27, 33–35], we also explore the relationship between these clinical measures and visual exploration patterns. We hypothesize that children exhibiting more symptomatology, having lower cognitive skills and lower adaptive scores will attend less to social areas and pre- sent less dynamic visual exploration, otherwise known as "*sticky attention*" [36, 37], to non-social areas.

**Table 1** Sample demographics

| N = 63 (!) | TD (n = 26) | ASD (n = 37) | *p* |
|---|---|---|---|
| Age | 3.60 ± 1.55 | 3.55 ± 1.21 | .888 |
| ADOS | | | |
| RRB[a] | 2.36 ± 2.06 | 8.08 ± 1.57 | < .001 |
| SA | 1.16 ± 0.72 | 6.16 ± 2.02 | < .001 |
| Total | 1.12 ± 0.44 | 6.81 ± 2.04 | < .001 |
| VABS-II | | | |
| Communication skills | 103.96 ± 10.97 | 75.92 ± 14.90 | < .001 |
| Socialization skills | 103.92 ± 10.49 | 75.76 ± 10.09 | < .001 |
| Daily living skills | 104.08 ± 8.22 | 75.95 ± 10.68 | |
| Motor skills | 104.33 ± 12.58 | 83.84 ± 11.41 | < .001 |
| Best estimate IQ[b] | 99.49 ± 11.04 | 62.94 ± 20.39 | < .001 |

[a] RRB severity score scale goes from 1 to 10 but doesn't include intermediate scores (2–3–4)

[b] Best Estimate IQ was obtained from either the Psycho-Educational Profile, third edition (PEP-3; [46], Mullen Scales of Early Learning (MSEL) [47] or the Wechsler Preschool and Primary Scale of Intelligence, fourth edition (WPPSI-IV)
[48] see Method section

## Method

### Sample

Initial total of acquired recordings for this task was 177. However, to ensure reasonable quality of data we decided to only include recordings where participants attended to both scenes for at least 50% of their total duration, leading to the exclusion of 74 recordings. The exclusion of these recordings led to an imbalanced sex-ratio between our groups including 38 TD females and only 2 females with ASD. Given previous results from Harrop et al. [27] showing sex differences in a similar task and the fact that we did not have enough female participants available for an equally sized sample, we only included males here. Our final sample included 63 preschool-aged males split in two age-matched group of 26 TD children aged 3.60 years (SD = 1.55) and 37 children with ASD aged 3.55 years (SD = 1.21, see Table 1). All children were included in the longitudinal Geneva Autism Cohort described in previous publications [14, 38–40]. Participants with ASD had received a clinical diagnosis of ASD according to the DSM-5 [1] before their inclusion in the study. In addition, all participants were assessed using the Autism Diagnostic Observation Schedule-G, or 2nd edition (ADOS) [41, 42] to re-con- firm their diagnoses using a standardized tool. Participants' parents provided written consent before the start of the evaluations in accordance with protocols approved by the institutional review board of the University of Geneva.

### Procedure and clinical measures

We applied the calibrated scores algorithm to our ADOS evaluation [43, 44] to quantify Restricted and Repetitive Behaviors (RRB), Social Affect (SA) and total symptom severity. These calibrated severity scores allow for the comparison of children with various developmental, language and cognitive levels regarding symptom severity and for a comparison between ADOS versions. All ADOS were administered by a trained examiner and scored with a qualified research reliable ADOS examiner. To assess adaptive functioning, examiners completed the Vine- land Adaptive Behavior Scales, second edition (VABS- II) [45] with participants' parents. To assess cognition, children were assessed using the Psycho-Educational Profile, third edition (PEP-3) [46], Mullen Scales of Early Learning (MSEL) [47] or the Wechsler Preschool and Primary Scale of Intelligence, fourth edition (WPPSI-IV)
[48] according to developmental level, chronological age and language skills. We subsequently used an approach described by Howlin et al. [49] and Kojovic et al. [38] to obtain a Best Estimate Intellectual Quotient (BEIQ) as an estimation of participants' cognitive skills at time of visit.

### Eye-tracking task and measures

Our eye-tracking task included two conditions:

- *the Parallel condition* (see Fig. 1a) showed two chil-dren playing independently on a xylophone for 56 s. The two children who figured in the video were told

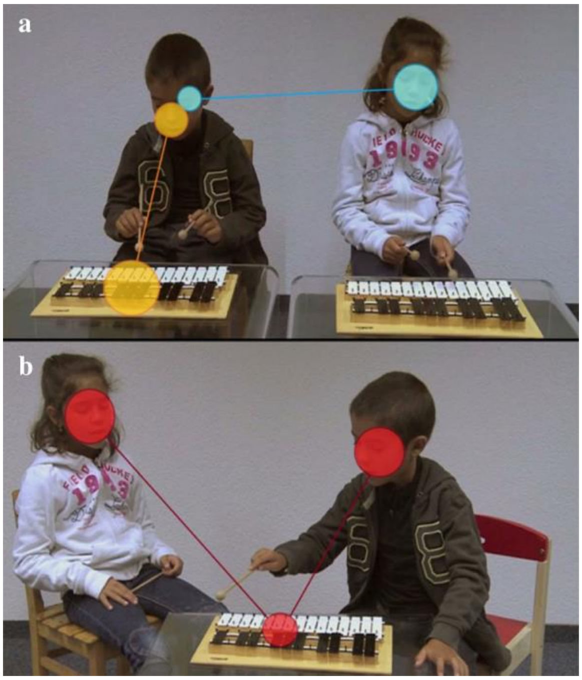



**Fig. 1** Eye-tracking stimuli. Dots and lines reproduce recorded gaze data. Dots represent fixations with size of the dots proportional to fixation duration. Lines between dots represent saccades. **a** Parallel play scene: orange dots reproduce F-O shift and blue dots reproduce F-F shift; **b** Interactive play scene: red dots reproduce F-O-F shift

to play as they wished and to look at the xylophone throughout the video. They were filmed separately to avoid subtle interactions and non-verbal communication passing between them. Videos were later edited into a film where they figured playing side by side.

- *the Interactive condition* (see Fig. 1b) showed the same two children taking turns on one xylophone together for a period of 60 s. Once again, they received no prior instructions before the filming, and they played freely together. During this condition, they sometimes looked at each other to establish turn-taking.

Children in the scenes were seven years old twins, a boy and a girl. We chose siblings because we wanted them to be used to playing together, so that their interactions would be as naturalistic as possible. Both scenes took place on a neutral white background to avoid distractions, and used the same material (table, mallets, xylophone). As children were playing the instrument, both scenes included musical tones but no verbal communication at all.

The task was administered using Tobii Studio software 3.1.6 on a TX300 eye-tracker which allows high-rate sampling (300 Hz) on a 1920 × 1200 pixel screen. Participants sat at approximately 60 cm from the screen, alone when possible or on a parent's lap if needed. After completing a five-point calibration designed specifically for young participants, they looked freely at the screen without any instructions. Fixations and saccades (see [50] for a detailed description) were later defined using the Tobii IV-T Fixation filter [51], which categorizes saccades and fixations using a velocity threshold of 30°/sec. Fixations that were shorter than 60 ms were discarded and adjacent fixations within 75 ms and a maximum of 0.5° were merged. An average of the right and left eyes was used to define fixations and the velocity calculator was set to 20 ms. Dynamic AOI were drawn on faces, bodies, objects (mallets and xylophone) and around the entire scene. From these AOI, we extracted and investigated several parameters, including percentage of fixations (the percentage of time spent in an AOI corrected for the total fixation time on a given scene), fixation duration (aver- aged using medians in order to reduce skewness while remaining representative of the distribution) and the number of gaze shifts. For the number of gaze shifts, we defined three potential types of gaze shifts between AOI: Face to Face shifts (F-F, see Fig. 1a) for quantifying participants' attempts at following non-verbal communication cues, Face to Objects shifts (F-O, see Fig. 1a) for quantifying joint attention behaviors, and Face to Objects to Face shifts (F-O-F, see Fig. 1b) reflecting three-step joint attention gaze shifting. "e number of gaze shifts were established using custom MATLAB v. 2018b scripts and data extracted from Tobii replays. Interrupted gaze (e.g., fixations on the background during shifts from one face to the other) or data that was lost when shifting from one AOI to another were discarded. Only complete data rep- resenting a fixation followed by a saccade and then a final fixation on the AOI as described above were included.

### Analysis strategy

Apart from the number of gaze shifts between AOI, which were calculated using custom MATLAB scripts, all analyses were conducted using IBM SPSS Statistics for MacIntosh, Version 24.0 (Armonk, NY:IBM Corp.) and graphs were plotted using Graphpad Prism 8.0 (Graph- Pad Software, La Jolla California USA, www.graphpad. com). To ensure that observed differences were not due to a difference in total time spent watching a scene between the groups, we first verified that both groups attended the scene for equal amounts of time. We investigated the effects of Condition (Parallel vs Interactive) and Diagnosis (ASD vs TD), as well as interactions between them in a 2 (Condition) × 2 (Diagnosis) design. We used repeated measures linear general model when investigating at percentages of time spent on AOI and fixation durations. When investigating the number of gaze shifts between AOI, we used a subsample of children, excluding children who did not look at least once at faces during both conditions ($n = 17$; ASD = 14, TD = 3) in order to specifically investigate how children with ASD, who generally demonstrate interest in faces, dynamically monitor others' actions. To investigate the effect of Condition and Diagnosis on gaze shifting, we performed generalized estimation equations with a Poisson distribution model. Finally, we performed Spearman correlations between clinical measures (ADOS severity scores, VABS-II scores and BEIQ) and eye-tracking measures to investigate potential relationships between ASD phenotype, adaptive functioning, cognitive skills and visual exploration pat- terns in the ASD group. When investigating correlations between the number of gaze shifts and clinical measures, we used the subsample of ASD children described above for the same reasons.

## Results

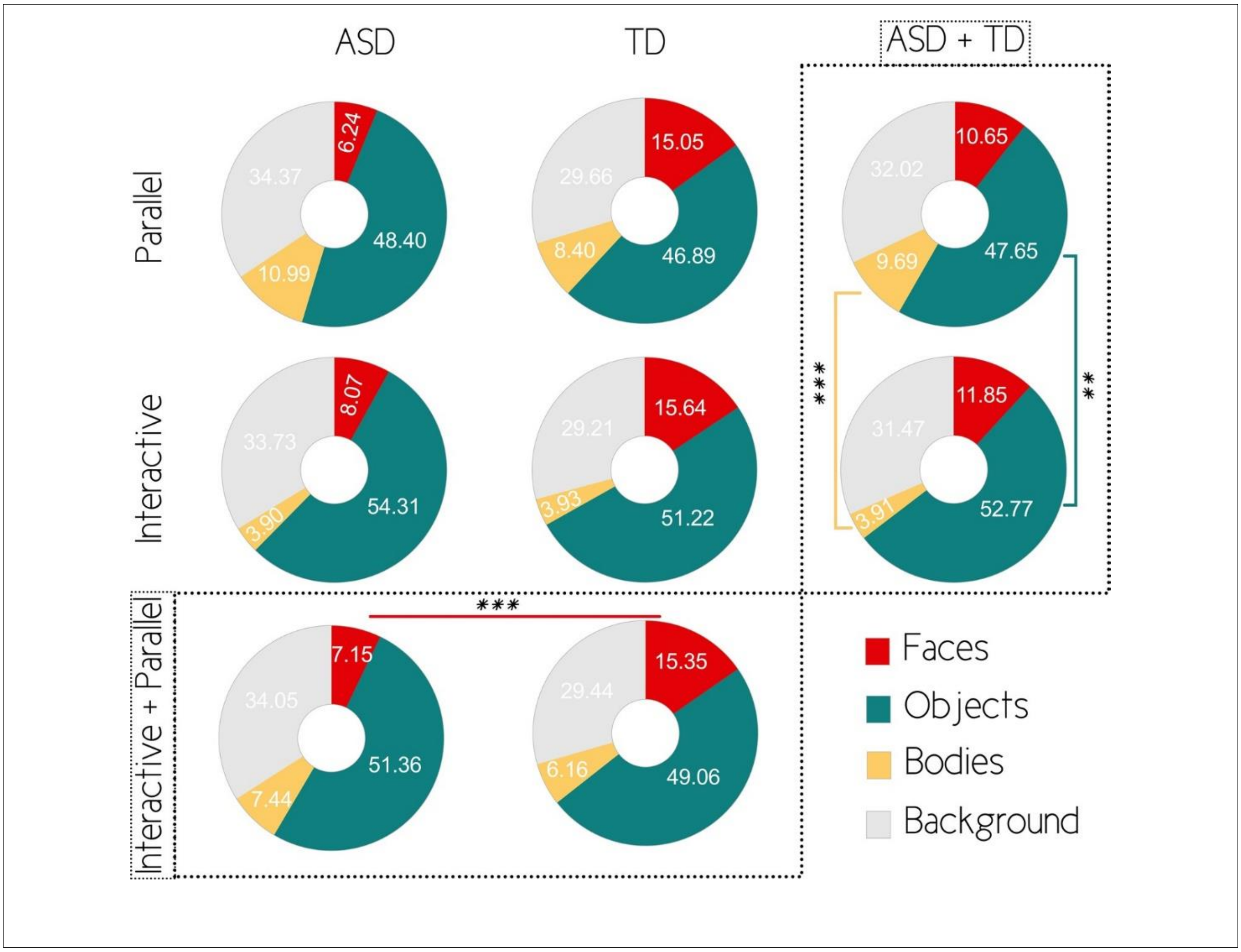
Our analyses revealed that the ASD and TD groups attended to both scenes for equivalent amounts of time, we did not identify an effect of diagnosis ($F(1,61) = 3.496$; $p > 0.05$) on the percentage of time spent looking at the scenes. However, we identified a main effect of condition ($F(1,61) = 4.307$; $p = 0.042$; $\eta p^2 = 0.066$), children attended to the interactive condition (mean = 81.918, SE = 1.301) slightly more than the parallel condition (mean = 78.248, SE = 1.548). Finally, we did not detect an interaction between diagnosis and condition ($F(1,61) = 1.071$; $p > 0.05$).

### Fixation percentage

Faces (see Table 2 and Fig. 2): We identified an effect of diagnosis on the time spent looking at faces ($F(1, 61) = 21.686$; $p < 0.001$, $\eta p^2 = 0.262$), with ASD children (mean = 7.138, SE = 1.135) looking less at faces compared

**Table 2** Repeated measures linear general model on fixation percentage

| Measure | Source | *df* | MS | F | *p* | ηp² | Observed power |
|---|---|---|---|---|---|---|---|
| Percentage on faces | | | | | | | |
| Within-subject effects | Condition | 1 | 44.460 | 1.431 | .236 | .023 | .218 |
| | Condition × Diagnosis | 1 | 11.925 | .384 | .538 | .006 | .094 |
| | Error | 61 | 31.065 | | | | |
| Between-subject effects | Intercept | 1 | 15,463.507 | 162.293 | .000 | .727 | 1.00 |
| | Diagnosis | 1 | 2066.291 | 21.686 | .000 | .262 | .996 |
| | Error | 61 | 95.281 | | | | |
| Percentage on objects | | | | | | | |
| Within-subject effects | Condition | 1 | 801.001 | 12.038 | .001 | .165 | .927 |
| | Condition × Diagnosis | 1 | 18.635 | .280 | .599 | .005 | .082 |
| | Error | 61 | 66.539 | | | | |
| Between-Subject Effects | Intercept | 1 | 308,032.209 | 608.601 | .000 | .909 | 1.00 |
| | Diagnosis | 1 | 148.333 | .293 | .590 | .005 | .083 |
| | Error | 61 | 506.132 | | | | |
| Percentage on bodies | | | | | | | |
| Within-subject effects | Condition | 1 | 1021.671 | 30.241 | .000 | .331 | 1.00 |
| | Condition × Diagnosis | 1 | 51.142 | 1.514 | .223 | .024 | .228 |
| | Error | 61 | 33.784 | | | | |
| Between-subject effects | Intercept | 1 | 5650.539 | 114.091 | .000 | .652 | 1.00 |
| | Diagnosis | 1 | 51.412 | 1.038 | .312 | .017 | .171 |
| | Error | 61 | 49.527 | | | | |
| Percentage on background | | | | | | | |
| Within-subject effects | Condition | 1 | 49.098 | .981 | .326 | .017 | .164 |
| | Condition × Diagnosis | 1 | 29.862 | .596 | .443 | .010 | .118 |
| | Error | 61 | 50.067 | | | | |
| Between-subject effects | Intercept | 1 | 121,231.963 | 558.888 | .000 | .906 | 1.00 |
| | Diagnosis | 1 | 799.603 | 3.686 | .672 | .060 | .471 |
| | Error | 61 | 216.916 | | | | |




to TD children (mean = 15.364, SE = 1.135). We did not identify any effect of condition (F(1,61) = 1.431; $p > 0.05$) nor an interaction between diagnosis and condition (F(1,61) = 0.384; $p > 0.05$).

Objects (see Table 2 and Fig. 2): We did not detect an effect of diagnosis regarding percentage of fixation on objects (F(1,61) = 0.293; $p > 0.05$). However, we identified a main effect of condition (F(1,61) = 12.038; $p = 0.001$; $\eta p^2 = 0.165$), where participants looked more at objects during interactive (mean = 52.776, SE = 2.209) compared to parallel condition (mean = 47.655, SE = 2.120). There was no interaction between diagnosis and condition (F(1,61) = 0.280; $p > 0.05$).

Bodies (see Table 2 and Fig. 2): We did not detect an effect of diagnosis on the percentage of fixations on bodies (F(1,61) = 1.038; $p > 0.05$). However, we identified a main effect of condition (F(1, 61) = 30.241; $p < 0.001$; $\eta p^2 = 0.331$), children looked less at bodies during interactive (mean = 3.909, SE = 0.417) compared to parallel condition (mean = 9.693, SE = 1.091). There was no interaction between diagnosis and condition (F(1,61) = 1.514; $p > 0.05$).

Background (see Table 2 and Fig. 2): We did not identify an effect of diagnosis (F(1,61) = 3.686, $p > 0.05$), condition (F(1,61) = 0.981; $p > 0.05$) or interaction (F(1,61) = 0.596; $p > 0.05$) between diagnosis and condition regarding the time spent looking at the background of the scenes.

### Fixation duration

Faces (see Table 3 and Fig. 3): We did not identify any effect of diagnosis (F(1, 52) = 0.239; $p > 0.05$). We however identified a main effect of condition (F(1, 52) = 17.766, $p < 0.001$; $\eta p^2 = 0.255$), fixations were longer during par- allel (mean = 0.341, SE = 0.012) compared to interactive condition (mean = 0.287, SE = 0.009). Finally, we did not identify any interaction between condition and diagnosis (F(1, 52) = 0.247; $p > 0.05$).

Objects (see Table 3 and Fig. 3): We did not identify any effect of diagnosis (F(1,55) = 0.019; $p > 0.05$). However we identified an effect of condition

**Table 3** Repeated measures linear general model on fixation duration

| Measure | Source | *df* | MS | F | *p* | ηp² | Observed power |
|---|---|---|---|---|---|---|---|
| Fixation duration on faces | | | | | | | |
| Within-subject effects | Condition | 1 | .77 | 17.766 | .000 | .255 | .985 |
| | Condition × Diagnosis | 1 | .001 | .247 | .621 | .005 | .078 |
| | Error | 52 | .004 | | | | |
| Between-subject effects | Intercept | 1 | 10.503 | 1382.020 | .000 | .964 | 1.00 |
| | Diagnosis | 1 | .002 | .239 | .627 | .005 | .077 |
| | Error | 52 | .008 | | | | |
| Fixation duration on objects | | | | | | | |
| Within-subject effects | Condition | 1 | .171 | 89.993 | .000 | .621 | 1.00 |
| | Condition × Diagnosis | 1 | .000 | .082 | .775 | .001 | .059 |
| | Error | 55 | .002 | | | | |
| Between-subject effects | Intercept | 1 | 3.505 | 1375.259 | .000 | .962 | 1.00 |
| | Diagnosis | 1 | .009 | 3.346 | .073 | .057 | .436 |
| | Error | 55 | .003 | | | | |
| Fixation duration on bodies | | | | | | | |
| Within-subject effects | Condition | 1 | .001 | .164 | .687 | .003 | .068 |
| | Condition × Diagnosis | 1 | .000 | .019 | .890 | .000 | .052 |
| | Error | 53 | .007 | | | | |
| Between-subject effects | Intercept | 1 | 5.957 | 696.078 | .000 | .929 | 1.00 |
| | Diagnosis | 1 | .002 | .207 | .651 | .004 | .073 |
| | Error | 53 | .009 | | | | |

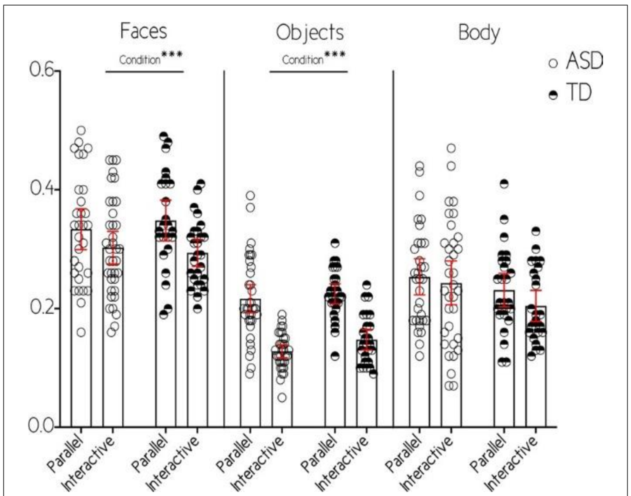



**Fig. 3** Fixation duration for each AOI in milliseconds. Lines represent variable main effects *$p$ < .05; **$p$ < .01; ***$p$ < .001

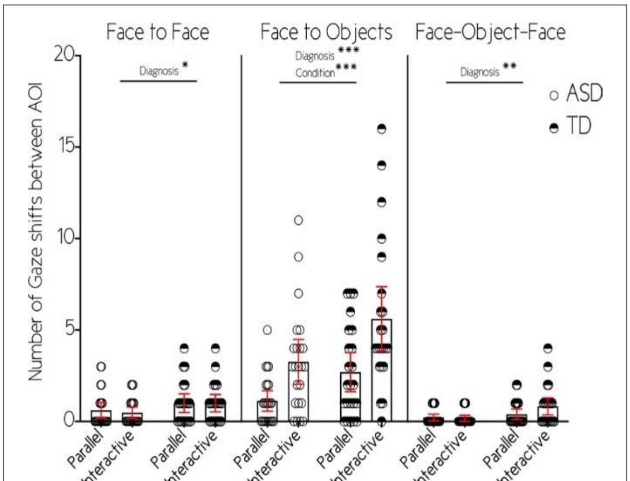



**Fig. 4** Number of gaze shifts between AOI. Lines represent main effects *$p$ < .05; **$p$ < .01; ***$p$ < .001

($F(1,55) = 89.993$; $p < 0.001$; $\eta p^2 = 0.066$), participants having shorter fixation on objects in the interactive condition (mean = 0.138, SE = 0.005) compared to parallel condition (mean = 0.216, SE = 0.007). Finally, there was no interaction between them regarding fixation duration on objects ($F(1,55) = 0.000$; $p > 0.05$).

Bodies (see Table 3 and Fig. 3): We did not identify an effect of diagnosis ($F(1,53) = 0.207$; $p > 0.05$), condition ($F(1,53) = 0.164$; $p > 0.05$) or any interaction ($F(1,53) = 0.019$; $p > 0.05$) regarding the fixation duration on bodies.

### Number of gaze shifts

F-F shifts (see Fig. 4): We observed an effect of diagnosis (Wald $\chi^2(1) = 6.549$; $p = 0.010$; $w = 0.333$) where children with ASD shifted less between faces overall compared to TD children. We did not observe a main effect of condition (Wald $\chi^2(1) = 0.255$; $p = 0.614$), or an interaction between diagnosis and condition (Wald $\chi^2(1) = 0.038$; $p = 0.846$).

F-O shifts (see Fig. 4): We identified an effect of diagnosis (Wald $\chi^2(1) = 13.030$; $p < 0.001$; $w = 0.470$), children with ASD shifted less between faces and objects compared to TD children. In addition, we identified a main effect of condition (Wald $\chi^2(1) = 29.440$; $p < 0.001$; $w = 0.706$), meaning that, in general, children shifted more between faces and objects during interactive compared to parallel condition. However, there was no interaction between diagnosis and condition (Wald $\chi^2(1) = 0.993$; $p = 0.319$).

F-O-F shifts (see Fig. 4): We identified a main effect of diagnosis (Wald $\chi^2(1) = 9.353$; $p = 0.002$; $w = 0.398$) where children with ASD made less F-O-F shifts compared to TD children. We did not observe a main effect of condition (Wald $\chi^2(1) = 0.474$; $p = 0.491$), or an interaction between diagnosis and condition (Wald $\chi^2$ $(1) = 1.520$; $p = 0.218$).

### Correlations between viewing patterns and clinical assessments

ADOS RRB: We identified a significant correlation between ADOS RRB severity scores and fixation duration on Objects in the interactive condition ($r_s = 0.457$; $p = 0.007$, see Table 4 and Fig. 5e) where increased fixation duration was associated with greater RRB symptoms. However, we did not identify any correlation between ADOS RRB severity scores and the fixation percentage on Faces, fixation percentage on Objects, fixation

**Table 4** Correlations between viewing patterns and clinical assessments

| | ADOS | | | Best Estimate IQ | Vineland-II | | | |
|---|---|---|---|---|---|---|---|---|
| | RRB | SA | Total | | Communication | Socialization | Daily living skills | Motor skills |
| Fixation percentage on faces | | | | | | | | |
| Parallel | −0.025 | −0.118 | −0.123 | −0.056 | 0.088 | 0.138 | 0.134 | 0.166 |
| Interactive | −0.215 | −0.207 | −0.228 | 0.126 | 0.355* | 0.342* | 0.316 | 0.163 |
| Fixation percentage on objects | | | | | | | | |
| Parallel | −0.105 | −0.120 | −0.165 | −0.128 | 0.066 | 0.004 | −0.060 | −0.143 |
| Interactive | −0.047 | −0.224 | −0.216 | 0.061 | 0.117 | −0.023 | 0.009 | −0.098 |
| Fixation percentage on bodies | | | | | | | | |
| Parallel | 0.183 | 0.296 | 0.276 | −0.083 | −0.304 | −0.043 | −0.200 | −0.090 |
| Interactive | 0.082 | 0.308 | 0.249 | −0.252 | −0.342* | 0.008 | −0.117 | 0.080 |
| Fixation duration on faces | | | | | | | | |
| Parallel | −0.140 | 0.257 | 0.159 | −0.034 | −0.218 | 0.013 | −0.092 | 0.142 |
| Interactive | 0.001 | 0.254 | 0.277 | 0.060 | −0.101 | 0.238 | 0.053 | 0.164 |
| Fixation duration on objects | | | | | | | | |
| Parallel | −0.034 | −0.044 | 0.015 | 0.213 | 0.223 | 0.242 | 0.161 | 0.145 |
| Interactive | 0.457** | 0.444* | 0.511** | −0.061 | −0.126 | −0.151 | −0.233 | −0.197 |
| Fixation duration on bodies | | | | | | | | |
| Parallel | −0.013 | −0.146 | −0.152 | 0.281 | 0.155 | −0.173 | 0.024 | 0.004 |
| Interactive | 0.232 | 0.312 | 0.414* | −0.089 | −0.171 | −0.099 | −0.112 | 0.008 |
| Face to Face shift | | | | | | | | |
| Parallel | 0.342 | −0.016 | 0.163 | 0.254 | 0.311 | 0.380 | 0.208 | −0.002 |
| Interactive | −0.309 | 0.004 | −0.081 | −0.128 | −0.168 | −0.031 | −0.202 | −0.168 |
| Face to Objects shift | | | | | | | | |
| Parallel | −0.113 | 0.060 | 0.087 | 0.396 | 0.365 | 0.285 | 0.294 | 0.265 |
| Interactive | −0.088 | −0.043 | 0.018 | 0.291 | 0.316 | 0.375 | 0.245 | 0.170 |
| Face-Object-Face shift | | | | | | | | |
| Parallel | −0.186 | 0.057 | −0.049 | 0.170 | 0.072 | −0.024 | 0.016 | 0.000 |
| Interactive | −0.203 | −0.133 | −0.141 | −0.173 | 0.017 | 0.286 | −0.043 | 0.026 |

* $p < .05$, **$p < .01$

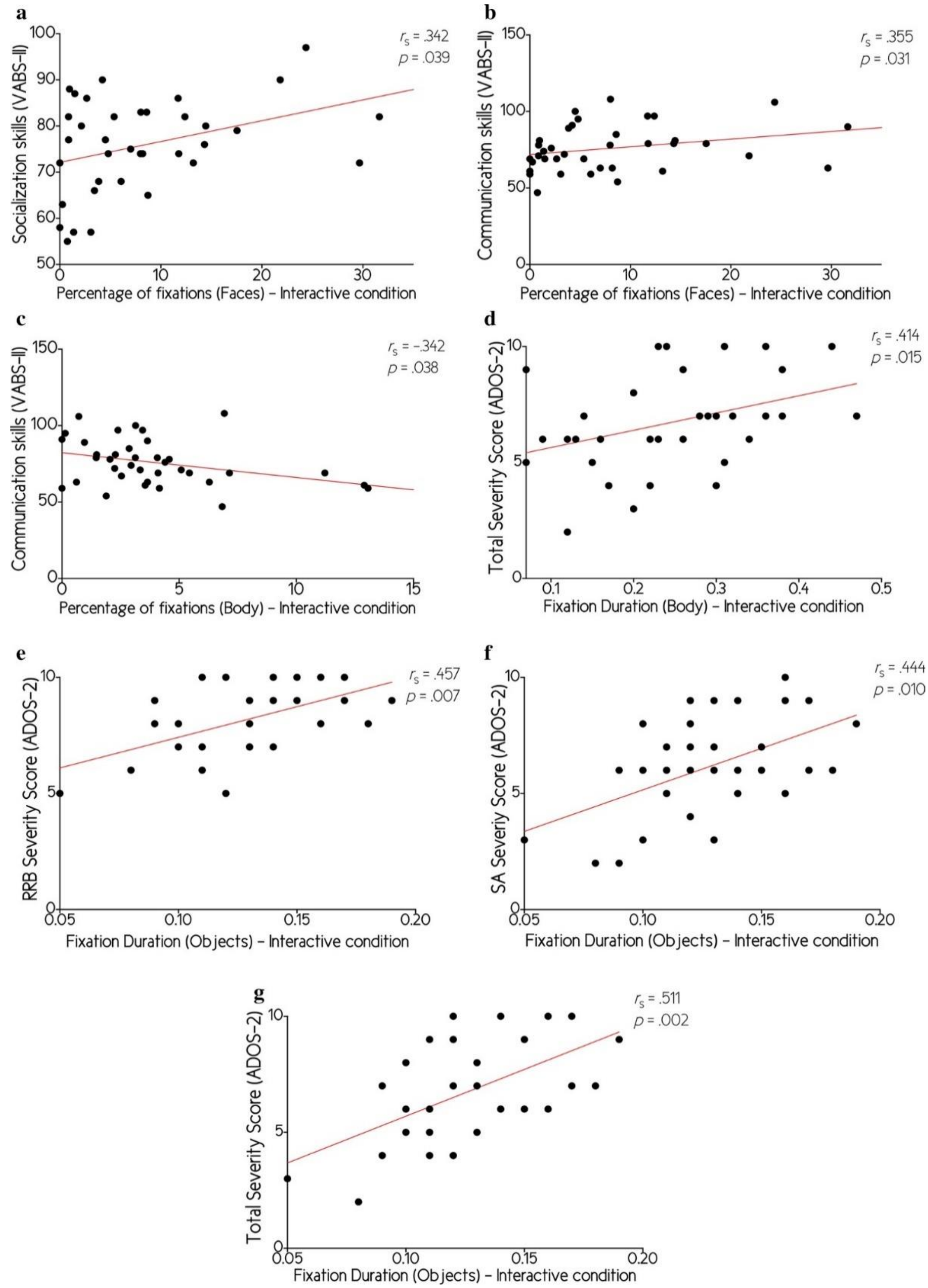



**Fig. 5** Correlations between eye-tracking and clinical variables. **a** Correlation between Socialization skills (VABS-II) and the percentage of fixations on faces in the Interactive condition; **b** Correlation between Communication skills (VABS-II) and the percentage of fixations on faces in the Interactive condition; **c** Correlation between Communication skills (VABS-II) and the percentage of fixations on bodies in the Interactive condition; **d** Correlation between Total severity score (ADOS-2) and fixation duration on bodies in the Interactive condition; **e** Correlation between Restricted and Repetitive Behavior severity score (ADOS-2) and fixation duration on objects in the Interactive condition; **f** Correlation between Social Affect severity score (ADOS-2) and fixation duration on objects in the Interactive condition; **g** Correlation between Total severity score (ADOS-2) and fixation duration on objects in the Interactive condition

percentage on Bodies, fixation duration on Faces, fixation duration on Objects in the parallel condition, fixation duration on Bodies, F-F shifts, F-O shifts, and F-O-F shifts (all $p > 0.05$, see Table 4).

ADOS SA: We identified a significant correlation between ADOS SA severity scores and fixation duration on Objects in the interactive condition ($r_s = 0.444$; $p = 0.010$, see Table 4 and Fig. 5f), where increased fixation duration was associated with greater SA symptoms. However, we did not identify any correlation between ADOS SA severity scores and the fixation percentage on Faces, fixation percentage on Objects, fixation per- centage on Bodies, fixation duration on Faces, fixation duration on Objects in the parallel condition, fixation duration on Bodies, F-F shifts, F-O shifts, and F-O-F shifts (all $p > 0.05$, see Table 4).

ADOS Total: We identified a significant correlation between ADOS Total severity scores and fixation duration on Objects in the interactive condition ($r_s = 0.511$; $p = 0.002$, see Table 4 and Fig. 5g) as well as fixation duration on Bodies in the interactive condition ($r_s = 0.414$; $p = 0.015$, see Table 4 and Fig. 5d) where increased fixation duration on were associated with greater symptoms overall. However, we did not identify any correlation between ADOS Total severity scores and the fixation per- centage on Faces, fixation percentage on Objects, fixation percentage on Bodies, fixation duration on Faces, fixation duration on Objects in the parallel condition, fixation duration on Bodies in the parallel condition, F-F shifts, F-O shifts, and F-O-F shifts (all $p > 0.05$, see Table 4).

BEIQ: We did not identify any significant correlation between BEIQ and any eye-tracking measure (all $p > 0.05$, see Table 4).

VABS Communication: We identified a significant correlation between VABS Communication scores and fixation percentage on Faces in the interactive condition ($r_s = 0.355$; $p = 0.031$, see Table 4 and Fig. 5b) as well as fixation percentage on Bodies in the interactive condition ($r_s = -0.342$; $p = 0.038$, see Table 4 and Fig. 5c) where increased fixation percentage on faces where associated with greater communication skills whereas increased fixation percentage on bodies where associated with lower communication skills. However, we did not identify any correlation between VABS Communication scores and the fixation percentage on Faces in the parallel condition, fixation percentage on Objects, fixation percentage on Bodies in the parallel condition, fixation duration on Faces, fixation duration on Objects, fixation duration on Bodies Faces, F-F shifts, F-O shifts, and F-O-F shifts (all $p > 0.05$, see Table 4).

VABS Socialization: We identified a significant correlation between VABS Socialization scores and fixation percentage on Faces in the interactive condition ($r_s = 0.342$; $p = 0.039$, see Table 4 and Fig. 5a) where increased fixation percentage on faces where associated with greater socialization skills. However, we did not identify any correlation between VABS Socialization scores and the fixation percentage on Faces in the parallel condition, fixation percentage on Objects, fixation percentage on Bodies, fixation duration on Faces, fixation duration on Objects, fixation duration on Bodies, F-F shifts, F-O shifts, and F-O-F shifts (all $p > 0.05$, see Table 4).

VABS Daily living skills: We did not identify any significant correlation between VABS Daily Living Skills scores and any eye-tracking measure (all $p > 0.05$, see Table 4).

VABS Motor skills: We did not identify any significant correlation between VABS Motor skills scores and any eye-tracking measure (all $p > 0.05$, see Table 4).

## Discussion

Our results demonstrate decreased social orienting towards faces in ASD compared to TD, which is commensurate with previous studies [2–9, 34, 52]. Similar to Harrop et al.'s results [27], our preschool boys with ASD showed reduced attention to faces compared to TD children. Watching a social interaction tended to increase time spent on faces in both groups in Harrop et al.'s study, an effect that we did not observe in our sample. Apart from a slight non-significant increase, watching a social interaction had no impact on the time spent looking at faces. A background difference used in the two studies may explain these contradictory results. While Harrop et al. [27] used a rich background that included various objects, the background we used was very neutral and did not include objects. A rich background could bias attention towards non-socially relevant elements, especially in individuals with ASD who present disrupted low-level perception, which can enhance spatial contrast sensitivity (for a review see [53]). Accordingly, the neutral background used in our study may have reduced potential distractions, leading to increased focus on the social elements of the scene even during the parallel condition. Furthermore, similar to previous studies (e.g. [22, 34]), we observed correlations between socialization and communication skills and percentage of fixations on faces exclusively during the interactive condition. Pre- schoolers who were attending more to faces also had stronger social and communication skills. ͏ese results reinforce the idea that ASD children's visual exploration of their social environment impacts the development of their socio-communicative skills. Moreover, this suggests that only during a socially complex task is the relation- ship between visual exploration patterns and socio-communicative deficits in children with ASD visible. Taken together, our results support interventions that are based on structured and neutral teaching environments, such as

Treatment and Education of Autistic and Communication-Handicapped Children for example (TEACCH) [54] which reduce environmental distractions and maintain a child's attention on the task at hand, but also reinforce the idea that social interaction tasks are most relevant in appraising social deficits in ASD [2].

We did not observe group differences pertaining to the percentage of time spent looking at objects, bodies or background. However, we observed a similar tendency in both groups to reduce the time spent on bodies in favor of time spent on objects when watching an inter- action compared to parallel play. This attentional shift, from bodies to objects, represents a direct consequence of increased social complexity and shared attention of the actors in the scene. Therefore, it was interesting to observe that, in our sample, shared attention of the actors during interactive play caused a similar visual focus on objects in both groups, whereas children with ASD showed decreased time spent looking at the shared activity in Shic et al.'s study [16]. There are several potential explanations for this discrepancy. The first, as previously discussed, might be related to the more visually complicated background in Shic et al.'s study, as children with ASD spent increased time looking at the more complicated background, consequently compromising the time spent looking at the activity. Second, an alternate explanation may relate to the fact that in Shic et al.'s study, the actors involved in the task (an adult and a child) inter- acted vocally, with the adult encouraging the child to solve a puzzle. By contrast, in our interactive condition, the children in the videos interacted non-verbally only by looking at each other. Moreover, unlike the puzzle in Shic's study, which is a silent game, our activity was playing a xylophone therefore producing musical tone. Considering that presenting a congruent sound induces faster orientation towards a target stimulus during a visual exploration task [55] and that children with ASD demonstrate atypical auditory processing with preserved or heightened abilities in musical processing [56, 57], the auditory component might have biased attentional focus in the two paradigms in different ways. Third, Shic et al. [16] proposed that children attend to elements that are within reach of their ability to comprehend, according to McCall and McGhee's [58] moderate discrepancy hypothesis, which could result in reduced attention to the shared activity especially in children with higher symptom severity. In contrast to Shic's task, the activity presented in our study might not have induced such a bias, given its simplicity. On a related note, we observed a negative correlation between communication skills and percentage of fixations on bodies, exclusively during the interactive condition. This suggests that the children who were less sensitive to context modulation and shared attention, who kept watching non-socially relevant elements of the scene, had decreased communication abilities. Taken together, our results suggest that ASD and TD's visual exploration patterns were both affected by social complexity but that a decreased sensitivity to this context modulation might impact the development of communication skills.

In addition to modify time spent on AOI, social complexity also impacted visual exploration patterns' dynamism. Indeed, despite a similar time spent on faces, social complexity impacted the fixation duration on faces in our sample where we observed a decrease of fixation duration in the interactive condition compared to the parallel one. In addition, children in our sample also decreased their fixation duration on objects during the interactive condition despite an increase of time spent on objects. On the other hand, while children decreased their time spent on bodies in the interactive condition, we did not observe any diminution of fixation duration on bodies. These results suggest that social complexity had a strong effect on the dynamic visual exploration on socially relevant AOI such as faces and objects but that it did not modify the visual exploration dynamism regarding non-socially relevant AOI such as bodies. Taken together, these results suggest that increased social complexity involves a modification of attentional engagement on social areas as reflected by the reduction of fixation duration. In our sample, children who displayed longer fixation on non-socially relevant AOI such as body had higher level of symptoms. Similarly, longer fixations on objects in the interactive condition were associated with a higher level of symptoms as well. Considering that several studies shown that children with ASD display visual disengagement difficulties [37], our results might suggest that attentional difficulties may well constitute a core symptom of ASD as children exhibiting more symptoms appear to be less sensitive to social complexity attentional modulation.

Per our hypothesis, decreased duration of fixations should have impacted participants' flexibility to become more active in their exploration between socially relevant AOI, consequently increasing the gaze shifts between faces as well as between faces and objects. However, although we only selected children with ASD with a minimal interest for faces, we still observed diminished social monitoring in our ASD group compared to our TD group, measured by the number of spontaneous Face to Face (F-F) shifts. This suggests that despite a minimal social orientation, children with ASD display an atypical dynamic exploration of social scenes. Conversely, we observed a similar number of F-F shifts regardless of the social context, suggesting that social monitoring is not modulated by context but is, rather, intrinsic in typical development. Considering the aforementioned positive relationship between socio-communicative skills and percentage of fixations on faces during interaction, this early decreased social monitoring observed in ASD might represent a basic alteration linked to impaired development of many higher social skills in ASD, such as shared intentionality [59, 60] or social oddity detection [61]. Given that most of these "higher" skills rely on the dynamic exploration of social interactions to identify relevant social cues, a decreased shift between faces, where most non-verbal communication occurs, is likely to have a detrimental effect on these skills.

While social complexity did not impact the number of F-F shift, we observed that children increased their Face to Objects (F-O) shifts, coherent with action monitoring and joint attention behaviors expected during an interactive play. Per our hypothesis, actors' shared attention on a common object in the interactive condition, increased its social saliency and increased the number of joint attention behaviors. However, joint attention behaviors were still less frequent in the ASD group compared to the TD group, as reported in most studies on joint attention and ASD [19, 21–24, 62]. An overall decrease in F-O gaze shifts supports joint attention deficits as a core feature of ASD. Nevertheless, it was encouraging to see that, despite these fundamental difficulties, social complexity still elicited a slight increase in joint attention behaviors in the ASD group. This supports some preserved joint attention abilities in ASD that are more apparent during the viewing of a richer social scene. Considering this, our results support studies and therapies that advocate for the inclusion of exaggerated emotional expressions and very rich social interactions during social interventions designed for children with ASD (e.g. Early Start Denver Model) [63] as they might recruit more of the children's skills.

Finally, we observed significantly less Face to Objects to Face (F-O-F) shifts, or three-step joint attention gaze shifting in our ASD group compared to our TD group. This three-step joint attention shifting reflects a greater level of complexity involving higher socio-cognitive skills. Considering that joint attention and social cognition are developmental processes [18, 21, 64] and that oculo- motor motricity depends on brain regions that develop during infancy [65, 66], it is very likely that three-steps joint attention shifts develop later after less sophisticated shifts have been mastered (e.g., F-O shifts). Therefore, the decreased occurrence of lower-level shifts observed in our ASD sample may explain why we observed few F-O-F shifts but also why social complexity did not increase these shifts overall. If we had included subjects with a wider age range in our ASD group, older children who demonstrate a TD-like frequency of two-step gaze shifts, we may have observed a more complex exploration of others' actions, including three-step gaze shifts that are modulated by context. Including older subjects as well could lead to a deeper understanding of the link between dynamic exploration patterns and the development of high-level social behaviors. Taken together, our results support joint attention as a pivotal ability in the development of higher socio-communicative skills during childhood and its importance as a key target in early interventions [67], for a review see [63, 68].

### Limitations

The main limitation of this study concerns its small sample size, which does not allow statistically robust conclusions to be drawn. Considering the small sample size, results should be taken with caution. Post-hoc power analyses were performed using the software package, G*Power3 [69] using the present sample size of 63, with 2 groups at an α of 0.05. ˇˇe recommended effect sizes used for this assessment were as follows: small (f= 0.10), medium (f= 0.25), and large (f= 0.40) [70]. The post hoc analyses revealed the statistical power for this study was 0.35 for detecting a small effect, 0.97 for detecting a medium effect and 0.99 for detecting a large effect size. In consequence, there was adequate power (> 0.80) at the medium and large effect size level but not enough statis- tical power to detect small effect sizes. Additional power analysis using similar parameters showed that in order to reach a power of 0.80 for small effect sizes, sample size should be increased to 200 participants.

Another limitation is the exclusion of females from our sample. Considering previous results showing that males with ASD consistently exhibit decreased attention to faces while females with ASD show TD-like attendance to faces when watching parallel play [27], it is important to keep in mind that our results apply only to males and can not be extended to females with ASD.

In our study, we quantified the number of gaze shifts and interpreted them as spontaneous joint attention behaviors or attempts at grasping non-verbal communication cues. Another way to analyze these gaze shifts could be to investigate whether they occur in coordination with non-verbal communication cues. This could provide information about whether higher levels of gaze shifting contingency with communication cues are related to better socio-communicative skills in ASD. However, this was not feasible in our study because there was no communication at all during the parallel play condition, making the analyses irrelevant. A possible workaround for future studies focusing on context modulation who would like to investigate this could be to manipulate levels of non-verbal communication behaviors between actors among conditions.

In spite of our efforts to control many aspects; including two children of the same age, a boy and a girl who look alike because they are twins, not changing the game proposed in both conditions, keeping the same furniture and the same room; the scenes differ in some aspects, such as the distance and the position of the children in the room. It is therefore not possible to exclude the fact that some of the results discussed in this article might be related to these changes.

Finally, we agree with the observation proposed by Parish-Morris et al. [29] who pointed out that screen-based eye-tracking studies are still lacking some ecological validity. Despite our efforts to propose paradigms as close as possible to everyday life, it is difficult to know whether the visual exploration patterns described in our study reflect authentic visual exploration of others' actions in a real-life situation. To remedy this, future studies could try live interactions using experimenters, or take advantage of new wearable eye-tracking devices, although feasibility remains questionable when applied to toddlers or preschoolers with ASD.

## Conclusion

This study uses a naturalistic design to study the visual exploration of others' actions, the primary source of social learning during early development. We manipulated context by presenting a socially simple scene of two children doing parallel play and a more complex social scene of the two children doing interactive play. We observed reduced attention to faces in the ASD group associated with decreased socio-communicative skills, and atypical dynamic exploration of others' actions as they exhibited less spontaneous gaze shifts suggesting reduced attention to non-verbal communication cues and lower joint attention skills. In addition, children who were less sensitive to social complexity attentional modulation showed longer fixations associated with higher level of ASD symptoms. The examination of spontaneous gaze shifts in a naturalistic design can help future understanding of how children with ASD dynamically process interactions to guide future interventions. This study supports interventions targeting the development of joint attention skills and the inclusion of engaging social interactions to reduce social deficits in ASD given the positive effects on visual exploration patterns of children with ASD of viewing interactive play compared to parallel play.

### Abbreviations

ADHD: Attention deficit-hyperactivity disorder; ADOS: Autism diagnostic observation schedule; AOI: Area of interest; ASD: Autism spectrum disorder; BEIQ: Best estimate intellectual quotient; F-F: Face to Face gaze shifts; F-O: Face to Objects gaze shifts; F-O-F: Face to Objects to Face gaze shifts; MSEL: Mullen Scales of Early Learning; PEP-3: Psycho-Educational Profile, third edition; RRB: Restricted and repetitive behavior; SA: Social affect; SD: Standard deviation; TD: Typical development; VABS-II: Vineland Adaptive Behavior Scales, second edition; WPPSI-IV: Wechsler Preschool and Primary Scale of Intelligence, fourth edition.

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### Authors' contributions

FR contributed to data collection, carried out statistical analyses and wrote the manuscript with inputs from all authors. NK, MF and SS contributed to data collection and commented on the manuscript. BG suggested the paradigm, aided in interpreting the results and commented on the manuscript. MF and MS conceived the paradigm used in the study. MS coordinated the study and helped shape the manuscript overall. All authors read and approved the final manuscript.

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### Availability of data and materials

The datasets analyzed during the current study includes sensitive data collected in a local sample. The risk of breaching patient confidentiality would be high; therefore, datasets are not publicly available but are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

Written consent was obtained from the parents of all participants included in the study. Swissethics - Commission d'éthique Suisse relative à la recherche sur l'être humain approved this study (Protocole 12-163/Psy 12-014), referred under the number PB_2016-01880.

### Consent for publication

Not applicable.

### Competing interests

On behalf of all authors, the corresponding author states that there is no conflict of interest.

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References


1. American Psychiatric Association. editor. Diagnostic and statistical man- ual of mental disorders : DSM-5. 5th ed. American Psychiatric Association; 2013.
2. Chevallier C, Parish-Morris J, McVey A, Rump KM, Sasson NJ, errington JD, Schultz RT. Measuring social attention and motivation in autism spectrum disorder using eye-tracking: stimulus type matters. Autism Res. 2015;8(5):620–8. https://doi.org/10.1002/aur.1479.
3. Guillon Q, Hadjikhani N, Baduel S, Rogé B. Visual social attention in autism spectrum disorder: insights from eye tracking studies. Neurosci Biobehav Rev. 2014;42:279–97. https://doi.org/10.1016/j.neubiorev.2014.03.013.
4. Jones EJH, Venema K, Earl R, Lowy R, Barnes K, Estes A, Dawson G, Webb SJ. Reduced engagement with social stimuli in 6-month-old infants with later autism spectrum disorder: a longitudinal prospective study of infants at high familial risk. J Neurodev Disord. 2016;8:7. https://doi.org/ 10.1186/s11689-016-9139-8.
5. Klin A, Jones W, Schultz R, Volkmar F, Cohen D. Visual fixation patterns during viewing of naturalistic social situations as predictors of social com- petence in individuals with autism. arch Gen Psychiatry. 2002;59(9):809–16. https://doi.org/10.1001/archpsyc.59.9.809.
6. Klin A, Lin DJ, Gorrindo P, Ramsay G, Jones W. Two-year-olds with autism orient to non-social contingencies rather than biological motion. Nature. 2009;459(7244):257. https://doi.org/10.1038/nature07868.
7. Parish-Morris J, Chevallier C, Tonge N, Letzen J, Pandey J, Schultz RT. Visual attention to dynamic faces and objects is linked to face processing skills: a combined study of children with autism and controls. Front Psychol. 2013. https://doi.org/10.3389/fpsyg.2013.00185.
8. Pierce K, Conant D, Hazin R, Stoner R, Desmond J. Preference for geomet- ric patterns early in life as a risk factor for autism. Arch Gen Psychiatry. 2011;68(1):101–9. https://doi.org/10.1001/archgenpsychiatry.2010.113.
9. Reisinger DL, Shaffer RC, Horn PS, Hong MP, Pedapati EV, Dominick KC, Erickson CA. Atypical social attention and emotional face processing in autism spectrum disorder: insights from face scanning and pupillometry. Front Integr Neurosci. 2020. https://doi.org/10.3389/fnint.2019.00076.
10. Speer LL, Cook AE, McMahon WM, Clark E. Face processing in chil- dren with autism: effects of stimulus contents and type. Autism. 2007;11(3):265–77. https://doi.org/10.1177/1362361307076925.
11. Chawarska K, Macari S, Shic F. Decreased spontaneous attention to social scenes in 6-month-old infants later diagnosed with autism spectrum disorders. Biol Psychiat. 2013;74(3):195–203. https://doi.org/10.1016/j. biopsych.2012.11.022.
12. Jones W, Klin A. Attention to eyes is present but in decline in 2–6-month- old infants later diagnosed with autism. Nature. 2013;504(7480):427. https://doi.org/10.1038/nature12715.
13. Sacrey L-A, Bryson SE, Zwaigenbaum L. Prospective examination of visual attention during play in infants at high-risk for autism spectrum disorder: a longitudinal study from 6 to 36 months of age. Behav Brain Res. 2013;256:441–50. https://doi.org/10.1016/j.bbr.2013.08.028.
14. Franchini M, Wood de Wilde H, Glaser B, Gentaz E, Eliez S, Schaer M. Brief report: a preference for biological motion predicts a reduction in symp- tom severity 1 year later in preschoolers with autism spectrum disorders. Front Psych. 2016. https://doi.org/10.3389/fpsyt.2016.00143.
15. Pierce K, Marinero S, Hazin R, McKenna B, Barnes CC, Malige A. Eye tracking reveals abnormal visual preference for geometric images as an early biomarker of an autism spectrum disorder subtype associated with increased symptom severity. Biol Psychiat. 2016;79(8):657–66. https://doi.org/10.1016/j.biopsych.2015.03.032.
16. Shic F, Bradshaw J, Klin A, Scassellati B, Chawarska K. Limited activ- ity monitoring in toddlers with autism spectrum disorder. Brain Res. 2011;1380:246–54. https://doi.org/10.1016/j.brainres.2010.11.074.
17. Dawson G, Munson J, Estes A, Osterling J, McPartland J, Toth K, Carver L, Abbott R. Neurocognitive function and joint attention ability in young children with autism spectrum disorder versus developmental delay. Child Dev. 2002;73(2):345–58. https://doi.org/10.1111/1467-8624.00411.
18. Mundy P. Joint attention and social-emotional approach behavior in children with autism. Dev Psychopathol. 1995;7(1):63–82. https://doi.org/ 10.1017/S0954579400006349.
19. Dawson G, Toth K, Abbott R, Osterling J, Munson J, Estes A, Liaw J. Early social attention impairments in autism: social orienting, joint attention, and attention to distress. Dev Psychol. 2004;40(2):271–83. https://doi.org/ 10.1037/0012-1649.40.2.271. Murray DS, Creaghead NA, Manning-Courtney P, Shear PK, Bean J, Prendeville J-A. The relationship between joint attention and language in children with autism spectrum disorders. Focus Autism Other Dev Disabil. 2008. https://doi.org/10.1177/1088357607311443.
20. Franchini M, Armstrong VL, Schaer M, Smith IM. Initiation of joint atten- tion and related visual attention processes in infants with autism spec- trum disorder: literature review. Child Neuropsychol. 2019;25(3):287–317. https://doi.org/10.1080/09297049.2018.1490706.
21. Falck-Ytter T, Fernell E, Hedvall ÅL, von Hofsten C, Gillberg C. Gaze perfor- mance in children with autism spectrum disorder when observing com- municative actions. J Autism Dev Disord. 2012;42(10):2236–45. https:// doi.org/10.1007/s10803-012-1471-6.
22. Higuchi T, Ishizaki Y, Noritake A, Yanagimoto Y, Kobayashi H, Nakamura K, Kaneko K. Spatiotemporal characteristics of gaze of children with autism spectrum disorders while looking at classroom scenes. PLoS ONE. 2017. https://doi.org/10.1371/journal.pone.0175912.
23. Thorup E, Nyström P, Gredebäck G, Bölte S, Falck-Ytter T, EASE Team. Reduced alternating gaze during social interaction in infancy is associ- ated with elevated symptoms of autism in toddlerhood. J Abnorm Child Psychol. 2018;46(7):1547–64. https://doi.org/10.1007/s10802-017-0388-0.
24. Campbell DJ, Shic F, Macari S, Chawarska K. Gaze response to dyadic bids at 2 years related to outcomes at 3 years in autism spectrum disorders: a subtyping analysis. J Autism Dev Disord. 2014;44(2):431–42. https://doi. org/10.1007/s10803-013-1885-9.
25. Chawarska K, Macari S, Shic F. Context modulates attention to social scenes in toddlers with autism. J Child Psychol Psychiatry. 2012;53(8):903–13. https://doi.org/10.1111/j.1469-7610.2012.02538.x.
26. Harrop C, Jones D, Zheng S, Nowell S, Schultz R, Parish-Morris J. Visual attention to faces in children with autism spectrum disorder: are there sex differences? Molecular Autism. 2019;10:28. https://doi.org/10.1186/ s13229-019-0276-2.
27. Macari S, Milgramm A, Reed J, Shic F, Powell KK, Macris D, Chawarska K. Context-specific dyadic attention vulnerabilities during the first year in infants later developing autism spectrum disorder. J Am Acad Child Adolesc Psychiatry. 2020. https://doi.org/10.1016/j.jaac.2019.12.012.
28. Parish-Morris J, Pallathra AA, Ferguson E, Maddox BB, Pomykacz A, Perez LS, Bateman L, Pandey J, Schultz RT, Brodkin ES. Adaptation to different communicative contexts: an eye tracking study of autistic adults. J Neu- rodev Disord. 2019;11(1):5. https://doi.org/10.1186/s11689-019-9265-1.
29. Livingston LA, Shah P, Milner V, Happé F. Quantifying compensatory strat- egies in adults with and without diagnosed

autism. Molecular Autism. 2020;11(1):15. https://doi.org/10.1186/s13229-019-0308-y.

30. Livingston LA, Happé F. Conceptualising compensation in neurodevel- opmental disorders: reflections from autism spectrum disorder. Neurosci Biobehav Rev. 2017;80:729–42. https://doi.org/10.1016/j.neubiorev.2017. 06.005.
31. Wass S, Jones E, Gliga T et al. Shorter spontaneous fixation durations in infants with later emerging autism. Sci Rep. 2015;5:8284. https://doi.org/ 10.1038/srep08284
32. Avni I, Meiri G, Bar-Sinai A, Reboh D, Manelis L, Flusser H, Michaelovski A, Menashe I, Dinstein I. Children with autism observe social interactions in an idiosyncratic manner. Autism Res. 2019. https://doi.org/10.1002/aur. 2234.
33. Murias M, Major S, Davlantis K, Franz L, Harris A, Rardin B, Sabatos-DeVito M, Dawson G. Validation of eye-tracking measures of social attention as a potential biomarker for autism clinical trials. Autism Res. 2018;11(1):166–74. https://doi.org/10.1002/aur.1894.
34. Shaffer RC, Pedapati EV, Shic F, Gaietto K, Bowers K, Wink LK, Erickson CA. Brief report: diminished gaze preference for dynamic social interaction scenes in youth with autism spectrum disorders. J Autism Dev Disord. 2017;47(2):506–13. https://doi.org/10.1007/s10803-016-2975-2.
35. Keehn B, Müller R-A, Townsend J. Atypical attentional networks and the emergence of autism. Neurosci Biobehav Rev. 2013;37(2):164–83. https://doi.org/10.1016/j.neubiorev.2012.11.014.
36. Sacrey L-AR, Armstrong VL, Bryson SE, Zwaigenbaum L. Impairments to visual disengagement in autism spectrum disorder: a review of experimental studies from infancy to adulthood. Neurosci Biobehav Rev. 2014;47:559–77. https://doi.org/10.1016/j.neubiorev.2014.10.011.
37. Kojovic N, Ben Hadid L, Franchini M, Schaer M. Sensory processing issues and their association with social difficulties in children with autism spec- trum disorders. J Clin Med. 2019. https://doi.org/10.3390/jcm8101508.
38. Robain F, Franchini M, Kojovic N, Wood de Wilde H, Schaer M. Predictors of treatment outcome in preschoolers with autism spectrum disorder: an observational study in the Greater Geneva Area Switzerland. J Autism Dev Disord. 2020. https://doi.org/10.1007/s10803-020-04430-6.
39. Sperdin HF, Coito A, Kojovic N, Rihs TA, Jan RK, Franchini M, Plomp G, Vulliemoz S, Eliez S, Michel CM, Schaer M. Early alterations of social brain networks in young children with autism. Elife. 2018;7:e31670. https://doi. org/10.7554/eLife.31670.
40. Lord C, Risi S, Lambrecht L, Cook EH, Leventhal BL, DiLavore PC, Pickles A, Rutter M. The autism diagnostic observation schedule-generic: a standard measure of social and communication deficits associated with the spectrum of autism. J Autism Dev Disord. 2000;30(3):205–23.
41. Lord C, Rutter M, DiLavore PC, Risi S, Gotham K, Bishop SL. Autism diag- nostic observation schedule, 2nd edition (ADOS-2). Western Psychologi- cal Services; 2012.
42. Gotham K, Pickles A, Lord C. Standardizing ADOS scores for a meas- ure of severity in autism spectrum disorders. J Autism Dev Disord. 2009;39(5):693–705. https://doi.org/10.1007/s10803-008-0674-3.
43. Hus V, Gotham K, Lord C. Standardizing ADOS domain scores : Separat- ing severity of social affect and restricted and repetitive behaviors. J Autism Dev Disord. 2014;44(10):2400–12. https://doi.org/10.1007/ s10803-012-1719-1.
44. Sparrow SS, Balla DA, Cicchetti DV. Vineland II: Vineland adaptive behavior scales. American Guidance Service; 2005.
45. Schopler E, Lansing MD, Reichler RJ, Marcus LM. Psychoeducational Pro- file: TEACCH individualized assessment for children with autism spectrum disorders. 3rd ed. Berlin: Pro-Ed, Inc.; 2005.
46. Mullen EM. Mullen Scales of Early Learning. AGS ed.; 1995.
47. Weschler D. Weschler preschool and primary scale of intelligence— fourth edition. Pearson; 2012.
48. Howlin P, Savage S, Moss P, Tempier A, Rutter M. Cognitive and language skills in adults with autism: a 40-year follow-up. J Child Psychol Psychiatry. 2014;55(1):49–58. https://doi.org/10.1111/jcpp.12115.
49. Land MF, Tatler BW. Looking and acting: vision and eye movements in natural behaviour (p. xi, 269). Oxford University Press; 2009. https://doi.org/10.1093/acprof:oso/9780198570943.001.0001.
50. Olsen A. The Tobii IVT Fixation Filter Algorithm description. https://www. semanticscholar.org/paper/The-Tobii-IVT-Fixation-Filter-Algorithm-descr iption-Olsen/66cdac4b380eabb9de3b25c7922c8de92d8d6cae#paper-header (2012).
51. Frazier TW, Strauss M, Klingemier EW, Zetzer EE, Hardan AY, Eng C, Young- strom EA. A meta-analysis of gaze differences to social and nonsocial information between individuals with and without autism. J Am Acad Child Adolesc Psychiatry. 2017;56(7):546–55. https://doi.org/10.1016/j. jaac.2017.05.005.
52. Mottron L, Dawson M, Soulières I, Hubert B, Burack J. Enhanced percep- tual functioning in autism: an update, and eight principles of autistic perception. J Autism Dev Disord. 2006;36(1):27–43. https://doi.org/10. 1007/s10803-005-0040-7.
53. Schopler E, Mesibov GB, Hearsey K. Structured teaching in the TEACCH system. In: Schopler E, Mesibov GB, editors. Learning and cognition in autism. Boston: Springer; 1995. p. 243–68. https://doi.org/10.1007/978-1- 4899-1286-2_13.
54. Iordanescu L, Grabowecky M, Franconeri S, Theeuwes J, Suzuki S. Char- acteristic sounds make you look at target objects more quickly. Atten Percept Psychophys. 2010;72(7):1736–41. https://doi.org/10.3758/APP. 72.7.1736.
55. Ocak E, Eshraghi RS, Danesh A, Mittal R, Eshraghi AA. Central auditory pro- cessing disorders in individuals with autism spectrum disorders. Balkan Med J. 2018;35(5):367–72. https://doi.org/10.4274/balkanmedj.2018.0853.Ouimet T, Foster NEV, Tryfon A, Hyde KL. Auditory-musical processing in autism spectrum disorders: a review of behavioral and brain imaging studies. Ann N Y Acad Sci. 2012;1252:325–31. https://doi.org/10.1111/j. 1749-6632.2012.06453.x.
56. McCall RB, McGhee PE. The discrepancy hypothesis of attention and affect in infants. In: Užgiris IČ, Weizmann F, editors. The structuring of experience. Springer; 1977. p. 179–210. https://doi.org/10.1007/ 978-1-4615-8786-6_7.
57. Tomasello M, Carpenter M. Shared intentionality. Dev Sci. 2007;10(1):121–5. https://doi.org/10.1111/j.1467-7687.2007.00573.x.
58. Tomasello M, Carpenter M, Call J, Behne T, Moll H. Understanding and sharing intentions: The origins of cultural cognition. Behav Brain Sci. 2005;28(5):675–91; discussion 691–735. https://doi.org/10.1017/S0140525X05000129.
59. Benson V, Castelhano MS, Howard PL, Latif N, Rayner K. Looking, seeing and believing in autism: eye movements reveal how subtle cognitive processing differences impact in the social domain. Autism Res. 2016;9(8):879–87. https://doi.org/10.1002/aur.1580.
60. Franchini M, Glaser B, Wood de Wilde H, Gentaz E, Eliez S, Schaer M. Social orienting and joint attention in preschoolers with autism spectrum disorders. PLoS ONE. 2017;12(6):e0178859. https://doi.org/10.1371/journal.pone.0178859.
61. Rogers SJ, Dawson G. Early Start Denver Model for young children with autism: promoting language, learning, and engagement. Guilford Press; 2010.
62. Mundy P. A review of joint attention and social-cognitive brain systems in typical development and autism spectrum disorder. Eur J Neurosci. 2018;47(6):497–514. https://doi.org/10.1111/ejn.13720.

63. Bruchhage MMK, Bucci MP, Becker EBE. Cerebellar involvement in autism and ADHD. In: Manto M, Huisman TAGM, editors. Handbook of clinical neurology, vol. 155. Elsevier; 2018. p. 61–72. https://doi.org/10.1016/ B978-0-444-64189-2.00004-4.
64. Freedman EG, Foxe JJ. Eye movements, sensorimotor adaptation and cerebellar-dependent learning in autism: toward potential biomarkers and subphenotypes. Eur J Neurosci. 2018;47(6):549–55. https://doi.org/ 10.1111/ejn.13625.
65. Kasari C, Gulsrud A, Freeman S, Paparella T, Hellemann G. Longitudinal fol- low up of children with autism receiving targeted interventions on joint attention and play RH = targeted interventions on joint attention and play. J Am Acad Child Adolesc Psychiatry. 2012;51(5):487–95. https://doi. org/10.1016/j.jaac.2012.02.019.
66. Murza KA, Schwartz JB, Hahs-Vaughn DL, Nye C. Joint attention interven- tions for children with autism spectrum disorder: a systematic review and meta-analysis. Int J Lang Commun Disord. 2016;51(3):236–51. https://doi. org/10.1111/1460-6984.12212.
67. Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sci- ences. Behav Res Methods. 2007;39(2):175–91. https://doi.org/10.3758/ BF03193146.
68. Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Earlbaum Associates; 1988.

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## 6.4 Full length article: Study 4

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# Measuring social orienting in preschoolers with autism spectrum disorder using cartoons stimuli

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ABSTRACT

Altered social orienting (SO) was proposed as the primary source of socio-communicative difficulties in autism spectrum disorder (ASD). Eye-tracking studies generally confirm a decreased SO in ASD population. However, SO has been scarcely investigated using minimally social stimuli such as cartoons. The extent to which SO might be decreased when watching cartoons is therefore unknown. Yet, it could allow for malleable and child-friendly paradigms that could be sensitive to early atypical visual preference. In this study, 90 preschoolers with ASD (age = 3.19 ± 0 .88) and 20 TD (age = 2.95 ± 1.26) watched two eye-tracking preference tasks. One *Realistic task*, displaying children dancing *versus* geometric shapes moving repetitively and a *Cartoon task*, displaying social and non-social cartoon stimuli with similar movements. We measured SO percentage along with refined visual exploration parameters and compared those of ASD children to TDs. In addition, we investigated their relations with behavioral measures such as symptom severity, developmental and adaptive levels. We evidenced a decreased SO percentage in ASD compared to TD children when watching the *Realistic task* but not the *Cartoon task*. We did not identify any other between groups differences. However, we identified several correlations between eye-tracking measures and developmental as well as adaptive measures within the *Cartoon task*. Together, our results support a preferential orientation of children with autism towards repetitively moving shapes but no decreased SO when measured with minimally social stimuli. Nonetheless, when investigating finer visual exploration parameters, even socially simple stimuli elicited atypical gaze patterns related to early developmental delay.

## 1. Introduction

In recent years, eye-tracking technology has become an increasingly relevant tool in the early screening of autism. Early screening currently remains one of the biggest challenges in autism research, particularly as it increases the chances of accessing early intervention, which in turn strongly influences the prognosis of children with autism (Dawson, 2008; Eldevik et al., 2009; Estes et al., 2015). While the age at diagnosis remains dramatically late, around 60 months of age according to a recent meta-analyses which included more than 30 studies and 66000 participants with ASD from 35 countries (van 't Hof et al., 2021), more and more studies suggest intervening during the first year of life (Green et al., 2017; Rogers et al., 2014; Whitehouse et al., 2021), before the appearance of first symptoms and in the absence of established markers, for children at high risk of autism (Ozonoff et al., 2011). This growing literature about ultra-early intervention illustrates the urgent need to develop screening tools for younger population. In this sense, eye-tracking might represent a prime candidate as it is the simplest way to obtain quantitative developmental information in infants and there- fore potential early markers. Indeed, unlike electroencephalography (EEG) or magnetic resonance imagery (MRI) which are time consuming and can be very difficult to administer, eye-tracking constitutes a very child-friendly tool allowing a multitude of original designs for the investigation of visual exploration patterns and their underlying mechanisms.

According to *"Social motivation theory" (*Chevallier et al., 2012; Dawson, 2008), the altered social orienting (SO) defined as the "psychological dispositions and biological mechanisms biasing the individual to preferentially orient to the social world" (Chevallier et al., 2012, p.231) might be at the very top of a cascade of social difficulties and

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altered social brain connectivity in autism. For instance, eye-tracking studies confirm atypical visual exploration of social stimuli in ASD illustrated by a reduced amount of time spent looking at the mouth and eyes when exploring faces compared to their TD peers (Falck-Ytter and von Hofsten, 2011; Klin et al., 2002). Some authors suggested investigating the preference of individuals with autism by using a simple split screen design opposing social to non-social stimuli. For instance, Pierce et al. (2011, 2016) evidenced that a subgroup of toddlers with ASD preferred to look at repetitively moving shapes rather than socially salient stimuli (here, kids moving/dancing). Using similar designs, other studies evidenced a preference for biological motion in typical development but not in ASD (Klin et al., 2009; see Todorova et al., 2019 for a meta-analysis). Interestingly, prospective studies suggested that decreased SO is already noticeable in 2-months old infants later diagnosed with ASD (E. J. H. Jones et al., 2016; W. Jones and Klin, 2013). Evidence for decreased SO early in life of people with ASD, before the appearance of first symptoms, is therefore generally accepted and could constitute a specific early marker that can be investigated through eye-tracking (see Chita-Tegmark, 2016 and Frazier et al., 2017 for meta-analyses). However, while most studies point to an overall decrease in SO at the group level (Franchini et al., 2016; Pierce et al., 2011), its use as an individual diagnostic marker remains limited as some children with ASD show levels of SO equivalent to TDs. In addition, the design of these studies presents many confounding factors (e.g., motion differences) that make it difficult to interpret the results in terms of social orienting. It is therefore relevant to keep developing eye-tracking tasks that could identify reduced SO early in life as it could constitute a stable and common marker of developing autism.

In this study, we propose an original task to measure social orienting. In this novel task we attempt to control for the confounding factors observed in preference tasks while remaining attractive and sensitive earlier in the course of development. To do this, we chose to develop a task using very simple stimuli in the form of cartoons. We hypothesized that the use of cartoons offers many advantages compared to more ecological tasks. A first potential benefit of using cartoons is that it could better capture the attention of toddlers, who are not always interested in the stimuli proposed in this kind of task (Masedu et al., 2021), since it is a very child-friendly material to which they might be more used to. In addition, the low ecological validity and complexity has been shown not to impact social information according to recent meta-analyses (Chi- ta-Tegmark, 2016) by reproducing decreased levels of SO in ASD. Yet, only two studies in this meta-analysis included cartoon material (Riby and Hancock, 2009; van der Geest et al., 2002). Riby & Hancock (2009) showed that individuals with ASD looked less at faces of both humans and actors compared to control. On the other side, van der Geest et al. (2002) showed that children with ASD looked at a social scene containing cartoons in the same way as typically developing children. Other studies investigating visual exploration of cartoons as social stimuli were mostly focusing on emotion recognition (Atherton and Cross, 2021; Pino et al., 2021; Rosset et al., 2010). Results from these studies differed and some put forward TD-like visual exploration when looking at cartoon stimuli (Atherton and Cross, 2021), while others pointed out an atypical visual exploration of both cartoon and realistic social stimuli (Rosset et al., 2010). Finally Pino et al. (2021) proposed a more nuanced results as they showed differences in visual exploration of realistic compared to avatar faces in specific emotions like surprise for example while other emotions such as happiness resulted in similar visual exploration between conditions. Whether or not an atypical visual exploration of social cartoon stimuli containing only minimal social information could be observed in ASD therefore remains debated. This is especially true since no study used cartoons stimuli in a social preference task so far. Investigating this question constitutes a crucial challenge in view of the growth of new technologies and the development of avatar-mediated interventions (e.g., Amat et al., 2021). Another potential advantage in using cartoons is that it allows us to control for confounding factors and notably motion. Indeed, it has been evidenced that biological movement is preferred by TDs but not by ASD individuals (Todorova et al., 2019) which might therefore constitute an inherent bias when presenting realistic social stimuli such as the ones in Pierce et al.'s (2011) study. In addition, the biological component is not the only factor to control for when it comes to motion. In fact, studies that proposed to look at a stimulus with either a repetitive or a random movement evidenced that children with ASD mostly preferred the repetitive one (Wang et al., 2018). Taken together, considering the attractiveness for repetitive motion and the absence of preference for biological motion in ASD, controlling for motion represents a major challenge when designing a task that aims to specifically measure SO. Here again the use of cartoons makes it easy to match movements when creating controlled and matched stimuli. We chose to propose a preference task design (i.e., split-screen) as it has been evidenced to be among the best one to elicit between group differences (Hedger et al., 2020; Kou et al., 2019). In addition to having already proven itself as a risk marker (Klin et al., 2009; Pierce et al., 2016), preference designs are easy to design, and metrics are intuitive and easy to understand. Finally, preference paradigms might also be easier to export to other media, like smartphones for example, compared to single scene exploration tasks. This last point might be crucial as more and more studies tend to use smartphones to develop eye-trackers (Chang et al., 2021; Strobl et al., 2019), placing smartphones as strategic screening tools in the near future.

In parallel to our original *Cartoon task* (see Fig. 1 a & b), we presented a *Realistic task* (see Fig. 1 c & d) inspired by Pierce et al.'s studies (2011, 2016) consisting in video-taped children moving/dancing side by side with geometric shapes (Franchini et al., 2016, 2017). The aim of presenting the two tasks in a single study was to see if our original *Cartoon task*, where minimally social stimuli and non-social stimuli were matched for motion, would result in SO levels that are similar to the *Realistic Task* which contains all confounding factors that we tried to control for in our original task. Despite differences in their respective design, we hypothesized that both tasks would result in reduced SO in children with ASD. We also hypothesized that the difference between groups would be larger in the *Realistic task* due to non-social stimuli being designed to be extremely attractive for individuals with ASD by displaying repetitively moving shapes that were previously reported as a frequent circumscribed interest in this population (Klin et al., 2007). Furthermore, based on previous studies (Falck-Ytter and von Hofsten, 2011; Franchini et al., 2016; Norbury et al., 2009; Pierce et al., 2016), we hypothesized that visual exploration parameters such as greater SO and more refined parameters such as shorter fixations, and greater social prioritization would correlate with lower levels of autistic symptoms as well as better developmental and adaptive skills.

## 2. Method

### 2.1. Sample

Participants in this study were part of the Geneva Autism cohort which aims to follow children longitudinally and described in previous publications (e.g., Franchini et al., 2016). The tasks of this study were presented to all children in the cohort between August 2020 and September 2021. Children with ASD received a clinical diagnosis according to the DSM-5 (American Psychiatric Association, 2013) and confirmed using the gold standard assessment (i.e. Autism Diagnosis Observation Schedule, 2nd edition, ADOS-2, Lord et al., 2012). Our initial sample included a total of 162 recordings from 31 TD children and 131 ASD children. From these recordings, 32 (6 TD and 26 ASD children) were removed because their screen attendance was lower than 50% of the task. This 50% threshold of minimal attendance to the task was decided according to what was done in the literature as it was used in Pierce et al.'s (2011) study, from which our tasks are greatly inspired. The records of children who did not pay attention to at least half of the task were therefore discarded. Additionally, 5 TD and 15 ASD children were removed to age match groups resulting in a final sample of 90 ASD

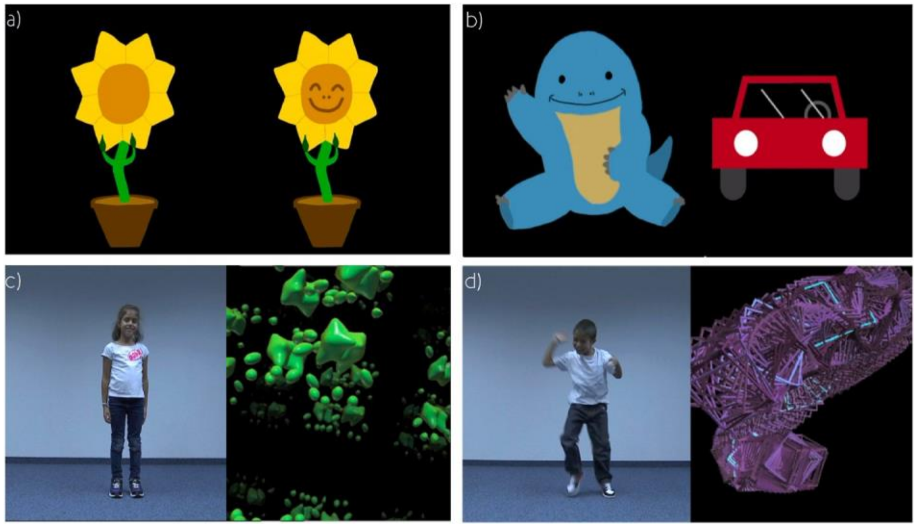


**Fig. 1.** Samples of stimuli from the *Cartoon* and *Realistic* tasks 1 **a)** Screenshot from the *Cartoon* task: Flowers moving as dancing **b)** Screenshot from the *Cartoon* task: monster waving and car whipping its windshield **c)** Screenshot from the *Realistic* task: little girl and geometric patterns moving **d)** Screenshot from the *Realistic* task: little boy and geometric patterns moving.

and 20 TD participants aged 3.19 ± 0.88 and 2.95 ± 1.26 respectively ($p$ = .313, see Table 1 for demographics of the sample). The investigation was carried out in accordance with the latest version of the Declaration of Helsinki. Participants' parents gave their written consent in accordance with protocols approved by the institutional review board of the University of Geneva.

### 2.2. Cartoon task

The task was presented on a 1920 × 1200 screen of 19ⁿⁿ and recorded using Tobii Studio software 3.1.6 and a TX300 Tobii eye-tracker. Participants sat at approximately 60 cm from the screen. Children who could not stay still sat on their parent's lap when possible. A five-point calibration for toddlers was administered at the beginning of the task and children were then looking freely at the screen.

The *Cartoon task* consisted in a 1-min visual preference task inspired from Pierce et al. (2011). It included a series of 10 stimuli opposing social and non-social cartoons in a split-screen fashion presented in a randomized order for 6 s each (see Fig. 1 a & b for samples and Supplementary Fig. 1 for whole stimuli). Each stimulus was created with matched and synchronized movements. A fixation circle appeared for 1 s between each stimulus to center participant's gaze. Areas of interest accounting for one half of the screen were drawn to delimit social and non-social sides of the screen.

**Table 1**
Main sample demographics.

| | | TD | ASD | p. |
|---|---|---|---|---|
| N = 110 | | $n$ = 20 | $n$ = 90 | |
| **Age** | | 2.95 ± 1.26 | 3.19 ± 0.88 | .313 |
| **ADOS** | RRB | 2.27 ± 2.20 | 9.09 ± 1.28 | <.001 |
| | SA | 1.18 ± 0.41 | 6.35 ± 1.96 | <.001 |
| | **Total** | 1.27 ± 0.47 | 7.53 ± 1.69 | <.001 |
| **MSEL** | Visual Reception | 118.38 ± 36.58 | 80.69 ± 24.88 | <.001 |
| | Fine Motor | 113.36 ± 42.19 | 78.28 ± 18.80 | <.001 |
| | Receptive Language | 112.77 ± 32.59 | 58.36 ± 33.95 | <.001 |
| | Expressive Language | 103.32 ± 32.48 | 56.02 ± 26.33 | <.001 |
| | **Total** | 111.96 ± 30.82 | 68.34 ± 23.18 | <.001 |
| **VABS-II** | Communication skills | 104.89 ± 8.70 | 77.68 ± 16.07 | <.001 |
| | Daily living skills | 99.50 ± 8.59 | 83.51 ± 11.54 | <.001 |
| | Socialization skills | 98.28 ± 7.30 | 79.09 ± 10.16 | <.001 |
| | Motor skills | 100.22 ± 9.52 | 87.66 ± 12.60 | <.001 |
| | **Total** | 100.44 ± 6.82 | 79.27 ± 11.76 | <.001 |

Note: (Mean ± SD).

### 2.3. Realistic task

Participants watched a second visual preference eye-tracking task also inspired by Pierce et al. (2011). This task, already described in (Franchini et al., 2016, 2017) opposed real human to geometric motion videos (see Fig. 1 c & d) during approximately 1 min. Like the *Cartoon task* AOIs were drawn on each side of the screen to delimit social and non-social. From the 90 ASD and 25 TD children, only 75 ASD and 15 TD children passed the minimum of 50% percent of time attending to the screen.

### 2.4. Eye-tracking measures

The different eye-tracking measures consisted in: the Total percentage of time which corresponds to the total time spent looking at the screen divided by the total time of the task; the Social Orienting (SO) percentage corresponding to the percentage of time spent looking at the social side of the screen; the Fixation durations on non-social/social each representing the mean fixation time on the specified AOI; the Number of fixations on non-social/social stimuli and finally the First fixation on social which corresponds to the number of first fixation toward the social side and therefore its prioritization. It was important for us to investigate for more refined visual exploration parameters as it could allow a better understanding of the underlying mechanisms when the exploration proves to be atypical.

### 2.5. Behavioral measures

In addition to eye-tracking measures, participants were assessed to measure their ASD symptom severity, developmental level, and adaptive skills. Regarding ASD level of symptoms, we used the ADOS-2 calibrated severity scores from (Gotham et al., 2009; Hus et al., 2014) which give Restricted and Repetitive Behaviors (RRB), Social Affect (SA) and Total severity scores. Regarding developmental levels, we used the Mullen Early Scale of Learning (MSEL, Mullen, 1995) to assess Visual Reception (VR), Expressive Language (EL), Receptive Language (RL), Fine Motricity (FM) and calculated developmental quotient by dividing the developmental levels by chronological age (Franchini et al., 2018; Robain et al., 2020) and multiplying by 100. Finally, adaptive skills levels were obtained using the Vineland Adaptive Behavior Scale, 2nd edition (VABS-II, Sparrow et al., 2005) which is a parental questionnaire targeting domains of Communication, Socialization, Daily living skills and Motor skills. The goal of these behavioral tests is to provide a better understanding of the relationship between developmental skills and visual exploration alterations for a better phenotyping.

### 2.6. Analysis strategy

All analyses were performed using IBM SPSS Statistics for MacIntosh, Version 24.0 (Armonk, NY: IBM Corp.), and plotted using GraphPad Prism 9 (GraphPad Software, La Jolla California USA, www.graphpad.com). As primary analyses, we compared TD and ASD groups on eye-tracking measures on both *Cartoon* and *Realistic* tasks using ANCOVAs, controlling for Age and Total percentage of time spent on screen plus SO percentage when comparing fixation durations and number of fixations. Considering previous studies showing reduced attention to social stimuli in ASD, we hypothesized that children within the TD group would exhibit more SO percentage compared to the ASD group in the *Realistic task*. Considering that stimuli were matched for motion but still opposed social versus non-social, we expected the same result but to a lesser extend within the *Cartoon task*.

In addition, we conducted a series of partial correlations between eye-tracking measures and behavioral measures, still controlling for the variables detailed above. Considering previous studies evidencing atypical fixations durations in ASD (e.g., Landry and Bryson, 2004) we hypothesized that finer gaze parameters such as increased fixation durations would be correlated with higher symptom severity as well as increased developmental and adaptive delay within the ASD group in both tasks.

All raw *p* values were corrected using Bonferroni correction for multiple correlations when analyzing subdomains from the same test. Therefore, ADOS SA and RRB p values were considered significant at .025; MSEL VR, MSEL LR, MSEL EL, MSEL FM as well as VABS-II Communication skills, Socialization, Daily living skills and Motor skills scores *p* values were considered significant at 0.0125.

## 3. Results

### 3.1. ANCOVAs

First, we investigated the extent to which the TD and ASD groups differed in their visual exploration of the two tasks presented. We compared the percentage of social orientation, the duration of fixations on social and non-social AOIs, the total number of fixations on social and non-social AOIs, and finally the number of first fixations towards social stimuli (see Table 2).

Cartoon task (see Table 2): There was no significant difference in any of the eye-tracking measures between TD and ASD when watching the *Cartoon task*. More specifically, ASD children's SO percentage was non-significantly different from TD children (F(1,106) = 1.278; $p > .05$; see Fig. 2), as well as for mean fixation duration on both social (F(1,105) = 0.003; $p > .05$) and non-social (F(1,105) = 0.164; $p > .05$) parts of the screen. Both groups made similar number of fixations on social (F (1,105) = 0.434; $p > .05$) and non-social (F(1,105) = 0.096; $p > .05$)

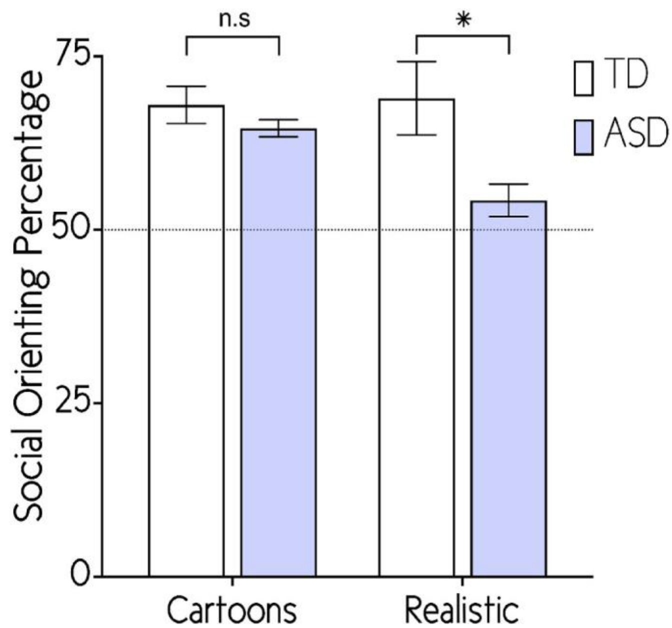


**Fig. 2.** Estimated marginal means (Age and Total percentage on screen as covariates) of Social Orienting percentage of TD and ASD groups watching the Cartoon and Realistic tasks.

parts of the screen and attended to social information on first fixation (F (1,106) = 0.050; $p > .05$) the same amount of time when watching the *Cartoon task*.

Realistic task (see Table 2): ASD children's SO percentage was significantly lower than the one from TD children when watching the *Realistic task* (F(1,86) = 6.390; $p = .013$; 1p$^2$ = 0.069; see Fig. 2). Other eye-tracking measures did not differ between groups. Both groups made the same number of fixations on social (F(1,85) = 0.161; $p > .05$), as well as on non-social side (F(1,85) = 0.202; $p > .05$). Fixation durations were also not significantly different between groups on both social (F(1,85) = 0.005; $p > .05$) and non-social side of the screen (F(1,85) = 0.517; $p > .05$). Finally, the number of first fixations towards social stimuli was equivalent between groups (F(1,86) = 0.269; $p > .05$).

### 3.2. Correlations

In order to provide better phenotyping, we examined the relationships between visual exploration impairments and developmental, adaptive skills and symptom severity in our sample (see Table 3). We first investigated if the SO percentages from the *Realistic* and *Cartoon task* were correlated together. We observed no significant correlation between the two SO percentages ($r_s = 0.154$, $p > .05$).

Within the TD group all correlations between behavioral and eye-tracking measures were non-significant (all $p > .05$, see Supplementary Table 1).

**Table 2**
Estimated Marginal means and Standard Error from ANCOVAs analyses within the Cartoon and Realistic task.

| | | Cartoon task | | | Realistic task | | |
|---|---|---|---|---|---|---|---|
| | | *ASD* | *TD* | *p.* | *ASD* | *TD* | *p.* |
| **Social Orienting percentage**[a] | | 64.66 (1.25) | 68.02 (2.69) | .261 | 54.27 (2.34) | 68.97 (5.30) | .013* |
| **Fixation duration**[b] | *Social* | 0.36 (0.01) | 0.36 (0.01) | .956 | 0.40 (0.01) | 0.40 (0.02) | .946 |
| | *Non-Social* | 0.36 (0.01) | 0.37 (0.02) | .687 | 0.42 (0.01) | 0.39 (0.02) | .474 |
| **Number o( fixations**[b] | *Social* | 72.81 (1.49) | 70.46 (3.21) | .511 | 66.50 (1.50) | 68.04 (3.49) | .690 |
| | *Non-Social* | 37.81 (0.89) | 37.15 (1.92) | .757 | 47.66 (1.19) | 49.03 (2.76) | .655 |
| **First fixation on social**[a] | | 4.15 (0.16) | 4.07 (0.35) | .823 | 5.27 (0.16) | 4.84 (0.35) | .269 |

[a] Covariates in the model include Age and Total percentage.

**Table 3**
Partial correlations matrix ($r$) between behavioral and eye-tracking measures within the ASD group.

| | | Cartoon Task | | | | | | Realistic Task | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Social Orienting percentage[b] | Fixation Duration[c] | | Number of Fixations[c] | | Number of first fixation on social[b] | Social Orienting Percentage[b] | Fixation Duration[c] | | Number of Fixations[c] | | Number of first fixation on social[b] |
| | | | Social | Non-Social | Social | Non-Social | | | Social | Non-Social | Social | Non-Social | |
| **ADOS** | Restricted and Repetitive Behavior | −.017 | .040 | .051 | −.048 | −.022 | −.034 | −.227 | −.008 | .094 | .026 | −.040 | −.050 |
| | SA | −.012 | .102 | .167 | −.053 | −.148 | −.078 | −.246 | .167 | .162 | −.108 | −.142 | −.036 |
| | **Total** | .016 | .144 | .146 | −.098 | −.127 | −.117 | −.349** | .148 | −.079 | −.079 | −.118 | −.065 |
| **MSEL** | Visual Reception | .249 | −.235 | −.106 | .274* | .067 | .226 | .286 | .025 | −.131 | −.100 | .093 | −.064 |
| | Fine Motor | .212 | −.220 | −.144 | .262 | .118 | .095 | .185 | −.049 | −.073 | −.040 | .054 | −.091 |
| | Receptive Language | .142 | −.366*** | −.247 | .348** | .219 | .245 | .227 | −.027 | −.087 | −.061 | .016 | −.087 |
| | Expressive Language | .228 | −.328** | −.283* | .288* | .256 | .194 | .133 | −.017 | −.077 | −.025 | −.003 | −.089 |
| | **Total** | .225* | −.332** | −.227* | .334** | .193 | .222* | .230 | −.018 | −.101 | −.063 | .040 | −.091 |
| **VABS-II** | Communication skills | .072 | −.390*** | −.301* | .351** | .252 | .271* | .140 | −.021 | .017 | −.048 | −.043 | −.069 |
| | Daily Living skills | .125 | −.349** | −.297* | .326** | .271* | .286* | .236 | −.234 | −.122 | .183 | .090 | −.198 |
| | Socialization skills | .073 | −.242 | −.129 | .234 | .099 | .248 | .095 | −.107 | −.079 | .064 | .060 | −.074 |
| | Motor skills | .091 | −.169 | −.030 | .192 | .029 | .210 | .118 | −.052 | −.099 | .052 | .134 | −.085 |
| | **Total** | .090 | −.323** | −.215* | .313** | .182 | .293** | .156 | −.098 | −.074 | .055 | .068 | −.119 |

*$p < .05$, **$p < .01$, ***$p < .001$ all raw $p$ values corrected using Bonferroni.
[b] Corrected for Age and Total percentage.
[c] Corrected for Age, Total percentage, and Social Orienting.

Within the ASD group, we identified several correlations between visual exploration parameters and behavioral measures in both tasks.

Cartoon task (see Table 3 and Fig. 3): We identified a positive correlation between the SO percentage and MSEL Total ($r(86) = 0.225$, $p = .035$, see Fig. 3 a). We also observed negative correlations between mean fixation duration on social information and MSEL RL ($r(85) = -0.366$, $p < .001$), MSEL EL ($r(85) = -0.328$, $p = .008$), MSEL Total ($r(85) = -0.332$, $p = .002$, see Fig. 3 b), VABS-II Communication skills ($r(85) = -0.390$, $p < .001$), VABS-II Daily Living skills ($r(85) = -0.349$, $p = .004$), and VABS-II Total ($r(85) = -0.323$, $p = .002$, see Fig. 3 g). Negative correlations between mean fixation duration on non-social information and MSEL EL ($r(85) = -0.283$, $p = .032$), MSEL Total ($r(85) = -0.227$, $p = .035$, see Fig. 3 c), VABS-II Communication skills ($r(85) = -0.301$, $p = .020$), VABS-II Daily Living skills ($r(85) = -0.297$, $p = .020$) and VABS-II Total ($r(85) = -0.215$, $p = .045$, see Fig. 3 h) were observed. Regarding the number of fixations, we identified positive correlations between the number of fixations on social information and MSEL VR ($r(85) = 0.274$, $p = .04$), MSEL RL ($r(85) = 0.348$, $p = .004$), MSEL EL ($r(85) = 0.288$, $p = .028$), MSEL Total ($r(85) = 0.334$, $p = .002$, see Fig. 3 d), VABS-II Communication skills ($r(85) = 0.351$, $p = .004$), VABS-II Daily living skills ($r(85) = 0.326$, $p = .008$) and VABS-II Total ($r(85) = 0.313$, $p = .003$, see Fig. 3 i). On the non-social side, we identified a positive correlation between the number of fixations on non-social information VABS-II Daily living skills ($r(85) = 0.271$, $p = .044$). Finally, We identified positive correlations between the number of first fixation on social information and MSEL Total ($r(86) = 0.222$,$p = .037$, see Fig. 3 e), VABS-II Communication skills ($r(86) = 0.271$, $p = .044$), VABS-II Daily Living skills ($r(86) = 0.286$, $p = .032$) and VABS-II Total ($r$

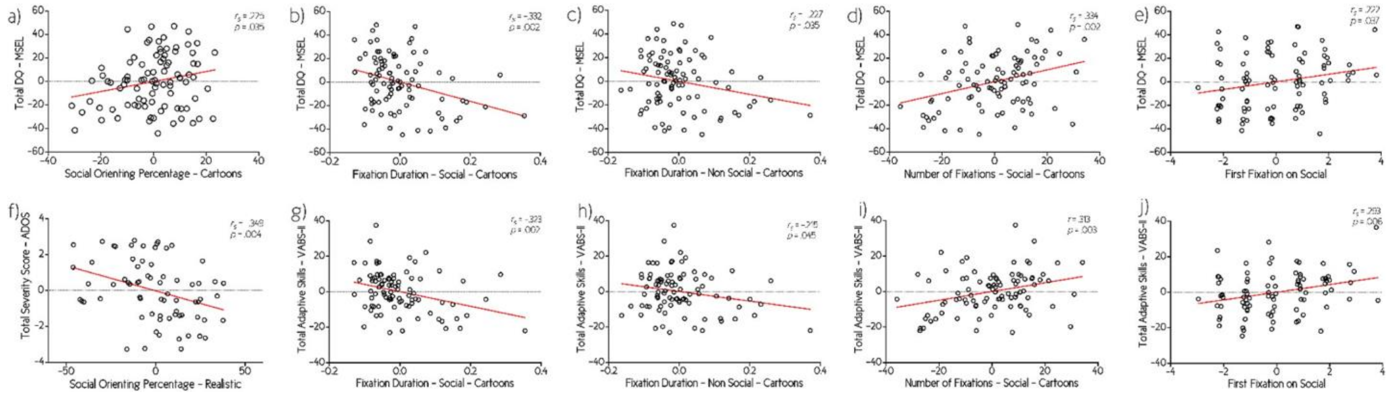

**Fig. 3.** Significant correlations between visual exploration parameters and behavioral measures **a)** Partial correlation between Social Orienting percentage unstandardized residuals when watching Cartoon task and MSEL Total DQ unstandardized residuals **b)** Partial correlation between fixation duration on social stimuli and MSEL Total DQ **c)** Partial correlation between fixation duration on non-social stimuli and MSEL Total DQ **d)** Partial correlation between number of fixations on social stimuli and MSEL Total DQ **e)** Partial correlation between first fixation on social and MSEL Total DQ **f)** Partial correlation between Social Orienting percentage unstandardized residuals when watching the Realistic task and ADOS Total Severity Score unstandardized residuals **g)** Partial correlation between fixation duration on social stimuli and VABS-II Total **h)** Partial Correlation between fixation duration on non-social stimuli and VABS-II Total **i)** Partial correlation between number of fixations on social stimuli and VABS-II Total **j)** Partial correlation between first fixation on social and VABS-II Total.(86) = 0.293, $p$ = .006, see Fig. 3 j). All remaining correlations were not significant (all p > .05, see Table 3).

Realistic task (see Table 3 and Fig. 3): We identified a negative correlation between the SO percentage and ADOS Total severity score ($r$ (71) = −0.349, $p$ = .004, see Fig. 3 f). All other correlations between eye-tracking parameters and behavioral measures were non-significant (all $p$ > .05, see Table 3).

## 4. Discussion

In this study, we aimed to measure social orienting (SO) in TD and ASD preschoolers using an original eye-tracking task displaying social vs non-social cartoon stimuli moving with similar patterns. In parallel, we presented children with a task inspired from Pierce et al. (2011) where video-taped moving/dancing kids are opposed to geometric patterns moving repetitively. As the second task was already used to measure SO in several studies (Franchini et al., 2016, 2017, 2018; Robain et al., 2020), the idea was to use it as a comparison point to see if, despite the very different stimuli, the two tasks generated similar results. Considering the Social Motivation framework (Chevallier et al., 2012), we hypothesized that we would find diminished SO in the ASD group on both tasks, though to a greater extent in the *Realistic task*. Overall, our results showed that ASD children exhibited diminished SO compared to TD children in the *Realistic task* but not in the *Cartoon task*. In addition, SO levels in the *Realistic task* were negatively correlated with ASD symptom severity reinforcing the idea that a preferential orientation towards geometric shapes is associated with increased symptom severity. Nevertheless, decreased SO levels, number of fixations, social prioritization as well as increased fixation duration when watching the *Cartoon task* were highly correlated with accentuated adaptive and developmental delay.

Our results corroborate those of Pierce et al. (2011) from whom our design is inspired. More specifically, ASD children showed a decreased attention to social stimuli compared to TD children in the *Realistic task*, supporting the idea of decreased SO as an early marker of autism (Chevallier et al., 2012). In contrast, our original *Cartoon task* does not distinguish TD children from ASD children based on their SO levels. Indeed, ASD children exhibited levels of SO similar to those observed in the TD group. Our two tasks, on the same children, thus indicate two opposite results, one suggesting an impaired SO and the other one a preserved SO in ASD. Although we expected a larger difference in the *Realistic task*, we were surprised by the absence of a SO difference within the *Cartoon task*. One can infer here that the great difference in the nature of the stimuli used in each task explains this dissociation between the tasks. The first point that can explain the differences between our tasks is that it is very likely that the geometric shapes presented in the *Realistic task* represent a biased competitor. Indeed, as introduced above, abstract shapes are parts of the circumscribed interests frequently re- ported in ASD (Klin et al., 2007). Yet, non-social stimuli that are of great interest for individuals ASD represent a greater attentional bias when compared to stimuli that are non-associated with restricted interests (Kwon et al., 2019; Unruh et al., 2016). In addition, a study evidenced that these repetitive shapes possess a high rewarding value in ASD children even when presented alone (Gale et al., 2019). A second point that could explain our diverging results is motion. Indeed, the *Realistic task* opposed biological motion, which is preferred in TD but not in ASD (Todorova et al., 2019) to repetitive movement which is generally preferred by ASD over random one (Wang et al., 2018). In contrast, we designed the stimuli of the *Cartoon task* to control for this effect by giving our stimuli similar repetitive patterns of movements. Considering previous literature, matching for motion in the *Cartoon task* might have helped reduce the preference gap compared to the *Realistic task*. A last and probably less impacting factor for the results differences between our tasks is that Cartoon social stimuli may be processed differently from real ones. Indeed, a review of the literature supports that people with ASD find anthropomorphic stimuli more socially stimulating than humans (Atherton and Cross, 2018). Other studies also evidenced higher SO towards cartoon faces rather than real faces in ASD (Saitovitch et al., 2013). Supporting these processing differences, studies in facial emotion recognition suggest a global processing, as observed in TD, within the ASD population when viewing cartoons while they use a local strategy in the presence of real faces (Brosnan et al., 2015; Rosset et al., 2010). On the other side, it has also been suggested that low ecological validity had no impact in SO paradigms (Chita-Tegmark, 2016) and studies report divergent results. For that matter, EEG studies evidenced atypical brain activity in ASD when watching cartoons compared to TD children (Jan et al., 2019; Sperdin et al., 2018). Taken all together, our results suggest that the *Realistic task* is an effective task to evidence group differences as it really captures the interest of children with ASD for repetitive moving geometric patterns. Yet, it might not represent the best measure of SO *per se* considering the stimuli used in it. Regarding the *Cartoon task,* we believe that it represents a more controlled measure of SO that currently does not support a generalized decreased SO in ASD. However, this conclusion can be nuanced considering that the factor with the largest size effect in SO studies is the presence of social interactions (i.e., social complexity). We can hypothesize that social stimuli presented in the *Cartoon task* were not socially complex enough for differences in SO to arise between groups. Consistent with this hypothesis, Pierce et al.'s (2016), qualified their task as inappropriate over 4 years of age. This age effect suggests that from the age of 4 the task was no longer challenging enough to bring out differences and that younger children may have not yet developed compensatory skills. Considering these, the same logic might apply to our original task and further investigation regarding the use of very simple stimuli should include even younger and/or high-risk infants as it may be more appropriate to such a younger age.

Despite equivalent levels of SO between the TD and ASD groups in the *Cartoon task*, we identified many correlations between visual exploration patterns and developmental and adaptive measures within this task. These correlations were specific to the *Cartoon task* and were not observed in the *Realistic task*. First, we evidenced that greater SO was positively correlated with developmental skills in our ASD sample. Considering that developmental delay is one of the first signs observable in children later diagnosed with ASD (Zwaigenbaum et al., 2005) it is relevant to observe this correlation. From those results one can infer that low levels of SO in the *Cartoon task*, just like Pierce et al.'s GeoPref, potentially constitute a red flag in infants concerning their develop- mental stage, even more in high-risk infants. Another interesting result lies in the relationship observed between longer fixation durations, resulting in less fixation, and greater developmental and adaptive delay. Just as developmental delay longer fixations are considered as one of the first symptoms of autism and are directly related to impaired visual disengagement skills reported in ASD (Landry and Bryson, 2004; Sacrey et al., 2014; Zwaigenbaum et al., 2005). For instance, Landry & Bryson (2004) evidenced among a sample of 5 years old children with ASD that their visual disengagement times were comparable to those of 2 months old TD infants, corresponding to the period of "obligatory looking". Considering that increased fixation durations have been linked to altered development of the neural attentional system (Frick et al., 1999) we hypothesize that the relationship between increased fixation durations and greater developmental delay reflect an overall neural developmental delay. Taken together, our results support that the presence of long fixations, and a lack of visual exploration often referred to as 'sticky attention' (Sacrey et al., 2013, 2014) when watching the *Cartoon task* should be considered as an additional red flag of early atypical development. Finally, it appeared in our results that children with decreased social prioritization (i.e, fewer first fixations on social, Fletcher-Watson et al., 2009), also showed greater developmental delays. These results are in lines with previous studies that reported later fixations on social stimuli within ASD literature (Fletcher-Watson et al., 2009; Freeth et al., 2010, 2011) and support that social stimuli are less attention-getting in the environment of individuals with ASD compared to TDs. While our initial results on SO did not support the Social Motivation theory, this decreased prioritization of social stimuli in ASD children associated with increased developmental delay indirectly supports it. To summarize, the various visual exploration parameters of the *Cartoon task* were highly correlated with developmental delay within preschoolers with ASD, but not so to ASD symptoms. Yet, considering that developmental delay as well as visual exploration atypicality are both early markers of autism, the presentation of the *Cartoon task* appears clinically relevant to identify potential red flags of atypical development and should be further explored in infants at high-risk for ASD. The existence of such relationships supports that even stimuli with minimal social information are enough to evidence gaze abnormalities and investigate their relationships with socio-developmental abilities in ASD. These results also emphasize the importance of investigating at refined visual parameters and their relationships with behavioral measures when presenting preference paradigms. By doing so it is possible to have a better over- view compared to only exploring the percentage of orientation which might bring a biased or partial information.

Our study includes some limitations. The first is the unequal number of participants in our sample groups. However, given the homogeneity of typical development compared to autism, this imbalance is not expected to impact the interpretation of the results. Another limitation of our study is related to the stimuli that could be different, for example could be more realistic avatars instead of cartoons or control for colors or other potential confounding factors that may have had an impact on the children's visual preferences. However, our choice of stimuli was motivated by a desire to match them for motion first and foremost, and in this sense, we believe that they effectively fulfill their role. Yet, other stimuli could be explored, especially more complex ones, while keeping this cartoon aspect. Furthermore, we feel that it is important for future studies including cartoon stimuli to continue to contrast them with more realistic stimuli but above all to include high-risk children to investigate visual preferences with this particular type of stimulus during the pro- drome of autism.

## 5. Conclusion

In this study, we presented TD and ASD preschoolers two visual preference eye-tracking tasks. The first one inspired from Pierce, the *Realistic*, involved real humans moving erratically *versus* abstract shapes with repetitive movements. The second task, the *Cartoon*, proposed simpler, cartoon stimuli with matched movements between stimuli. Our goal was to measure social attention, suggested as an early marker of ASD, using socially simple stimuli while comparing it to a relatively established task. Our results evidenced that ASD children had lower levels of SO than TD children in the *Realistic* task but equivalent in the *Cartoon* task. This result suggests a preserved SO in preschoolers with ASD when viewing minimally social and more controlled stimuli. Yet, our results highlighted that the *Cartoon* task efficiently captured the developmental and adaptive delay by showing numerous correlations with visual exploration parameters such as social prioritization, fixation duration and percentage of social orientation. Considering that developmental delay and gaze abnormalities represent early markers of autism, the *Cartoon* task, and overall, minimally social stimuli, might constitute a useful tool for early screening.

### Declaration of interest

None.


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### Authors' contribution

François Robain: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft, Visualization; Michel Godel, Fiona Journal and Nada Kojovic: Investigation, Writing - Review & Editing, Visualization; Martina Franchini: Conceptualization, Method- ology, Writing - Review & Editing, Visualization; Marie Schaer: Conceptualization, Methodology, Resources, Writing - Review & Editing, Visualization, Supervision, Funding acquisition.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi. org/10.1016/j.jpsychires.2022.10.039.

## References

Amat, A.Z., Zhao, H., Swanson, A., Weitlauf, A.S., Warren, Z., Sarkar, N., 2021. Design of an interactive virtual reality system, InViRS, for joint attention practice in autistic children. IEEE Trans. Neural Syst. Rehabil. Eng.: Publ. IEEE Eng. Med. Biol. Soc. 29, 1866–1876. https://doi.org/10.1109/TNSRE.2021.3108351.
American Psychiatric Association, 2013. In: Diagnostic and Statistical Manual of Mental Disorders: DSM-5, fifth ed. American Psychiatric Association.
Atherton, G., Cross, L., 2018. Seeing more than human: autism and anthropomorphic theory of mind. Front. Psychol. 9 https://doi.org/10.3389/fpsyg.2018.00528.
Atherton, G., Cross, L., 2021. Reading the mind in cartoon eyes: comparing human versus cartoon emotion recognition in those with high and low levels of autistic traits.
Psychol. Rep., 33294120988135 https://doi.org/10.1177/0033294120988135.
Brosnan, M., Johnson, H., Grawmeyer, B., Chapman, E., Benton, L., 2015. Emotion recognition in animated compared to human stimuli in

Franchini, M., Wood de Wilde, H., Glaser, B., Gentaz, E., Eliez, S., Schaer, M., 2016. Brief report: a preference for biological motion predicts a reduction in symptom severity 1 Year later in preschoolers with autism spectrum disorders. Front. Psychiatr. 7 https://doi.org/10.3389/fpsyt.2016.00143.
Franchini, M., Zo.ller, D., Gentaz, E., Glaser, B., Wood de Wilde, H., Kojovic, N., Eliez, S.,
Schaer, M., 2018. Early adaptive functioning trajectories in preschoolers with autism spectrum disorders. J. Pediatr. Psychol. 43 (7), 800–813. https://doi.org/10.1093/ jpepsy/jsy024.
Frazier, T.W., Strauss, M., Klingemier, E.W., Zetzer, E.E., Hardan, A.Y., Eng, C., Youngstrom, E.A., 2017. A meta-analysis of gaze differences to social and nonsocial information between individuals with and without autism. J. Am. Acad. Child Adolesc. Psychiatr. 56 (7), 546–555. https://doi.org/10.1016/j.jaac.2017.05.005.
Freeth, M., Chapman, P., Ropar, D., Mitchell, P., 2010. Do gaze cues in complex scenes capture and direct the attention of high functioning adolescents with ASD? Evidence from eye-tracking. J. Autism Dev. Disord. 40 (5), 534–547. https://doi.org/10.1007/ s10803-009-0893-2.
Freeth, M., Foulsham, T., Chapman, P., 2011. The influence of visual saliency on fixation patterns in individuals with Autism Spectrum Disorders. Neuropsychologia 49 (1), 156–160. https://doi.org/10.1016/j.neuropsychologia.2010.11.012.
Frick, J.E., Colombo, J., Saxon, T.F., 1999. Individual and developmental differences in disengagement of fixation in early infancy. Child Dev. 70 (3), 537–548. https://doi. org/10.1111/1467-8624.00039.
Gale, C.M., Eikeseth, S., Klintwall, L., 2019. Children with autism show atypical preference for non-social stimuli. Sci. Rep. 9, 10355 https://doi.org/10.1038/ s41598-019-46705-8.
Gotham, K., Pickles, A., Lord, C., 2009. Standardizing ADOS scores for a measure of severity in autism spectrum disorders. J. Autism Dev. Disord. 39 (5), 693–705. https://doi.org/10.1007/s10803-008-0674-3.
Green, J., Pickles, A., Pasco, G., Bedford, R., Wan, M.W., Elsabbagh, M., Slonims, V., Gliga, T., Jones, E., Cheung, C., Charman, T., Johnson, M., 2017. Randomised trial of a parent-mediated intervention for infants at high risk for autism: longitudinal outcomes to age 3 years. J. Child Psychol. Psychiatry Allied Discip. 58 (12), 1330–1340. https://doi.org/10.1111/jcpp.12728 amp; British Autism Study of Infant Siblings (BASIS) Team.
Hedger, N., Dubey, I., Chakrabarti, B., 2020. Social orienting and social seeking behaviors in ASD. A meta analytic investigation. Neurosci. Biobehav. Rev. 119, 376–395. https://doi.org/10.1016/j.neubiorev.2020.10.003.
Hus, V., Gotham, K., Lord, C., 2014. Standardizing ADOS domain scores: separating severity of social affect and restricted and repetitive behaviors. J. Autism Dev. Disord. 44 (10), 2400–2412. https://doi.org/10.1007/s10803-012-1719-1.
Jan, R.K., Rihs, T.A., Kojovic, N., Sperdin, H.F., Franchini, M., Custo, A., Tomescu, M.I., Michel, C.M., Schaer, M., 2019. Neural processing of dynamic animated social interactions in young children with autism spectrum disorder: a high-density electroencephalography study. Front. Psychiatr. 10, 582. https://doi.org/10.3389/
Landa, R., Rogers, S.J., Sigman, M., Stone, W.L., 2011. Recurrence risk for autism spectrum disorders: a baby siblings research consortium study. Pediatrics 128 (3),

adolescents with autism spectrum disorder. J. Autism Dev. Disord. 45 (6), 1785–1796. https://doi.org/ 10.1007/s10803-014-2338-9.
Chang, Z., Di Martino, J.M., Aiello, R., Baker, J., Carpenter, K., Compton, S., Davis, N., Eichner, B., Espinosa, S., Flowers, J., Franz, L., Harris, A., Howard, J., Perochon, S., Perrin, E.M., Krishnappa Babu, P.R., Spanos, M., Sullivan, C., Walter, B.K., et al., 2021. Computational methods to measure patterns of gaze in toddlers with autism spectrum disorder. JAMA Pediatr. 175 (8), 827–836. https://doi.org/10.1001/ jamapediatrics.2021.0530.
Chevallier, C., Kohls, G., Troiani, V., Brodkin, E.S., Schultz, R.T., 2012. The social motivation theory of autism. Trends Cognit. Sci. 16 (4), 231–239. https://doi.org/10.1016/j.tics.2012.02.007.
Chita-Tegmark, M., 2016. Social attention in ASD: a review and meta-analysis of eye-tracking studies. Res. Dev. Disabil. 48, 79–93. https://doi.org/10.1016/j.ridd.2015.10.011.
Dawson, G., 2008. Early behavioral intervention, brain plasticity, and the prevention of autism spectrum disorder. Dev. Psychopathol. 20 (3), 775–803. https://doi.org/ 10.1017/S0954579408000370.
Eldevik, S., Hastings, R.P., Hughes, J.C., Jahr, E., Eikeseth, S., Cross, S., 2009. Meta-analysis of early intensive behavioral intervention for children with autism. J. Clin. Child Adolesc. Psychol. 38 (3), 439–450. https://doi.org/10.1080/15374410902851739.
Estes, A., Munson, J., Rogers, S.J., Greenson, J., Winter, J., Dawson, G., 2015. Long-term outcomes of early intervention in 6-year-old children with autism spectrum disorder.
J. Am. Acad. Child Adolesc. Psychiatr. 54 (7), 580–587. https://doi.org/10.1016/j.jaac.2015.04.005.
Falck-Ytter, T., von Hofsten, C., 2011. How special is social looking in ASD: a review. Prog. Brain Res. 189, 209–222. https://doi.org/10.1016/B978-0-444-53884-0.00026-9.
Fletcher-Watson, S., Leekam, S.R., Benson, V., Frank, M.C., Findlay, J.M., 2009. Eye- movements reveal attention to social information in autism spectrum disorder. Neuropsychologia 47 (1), 248–257. https://doi.org/10.1016/j.neuropsychologia.2008.07.016.
Franchini, M., Glaser, B., Wood de Wilde, H., Gentaz, E., Eliez, S., Schaer, M., 2017. Social orienting and joint attention in preschoolers with autism spectrum disorders. PLoS One 12 (6), e0178859. https://doi.org/10.1371/journal.pone.0178859.

fpsyt.2019.00582.
Jones, E.J.H., Venema, K., Earl, R., Lowy, R., Barnes, K., Estes, A., Dawson, G., Webb, S. J., 2016. Reduced engagement with social stimuli in 6-month-old infants with later autism spectrum disorder: a longitudinal prospective study of infants at high familial risk. J. Neurodev. Disord. 8, 7. https://doi.org/10.1186/s11689-016-9139-8.
Jones, W., Klin, A., 2013. Attention to eyes is present but in decline in 2–6-month-old infants later diagnosed with autism. Nature 504 (7480), 427. https://doi.org/10.1038/nature12715.
Klin, A., Danovitch, J., Merz-Beyus, A., Volkmar, F., 2007. Circumscribed interests in higher functioning individuals with autism spectrum disorders: an exploratory study. Res. Pract. Persons Severe Disabil. 32, 89–100. https://doi.org/10.2511/rpsd.32.2.89.
Klin, A., Jones, W., Schultz, R., Volkmar, F., Cohen, D., 2002. Visual fixation patterns during viewing of naturalistic social situations as predictors of social competence in individuals with autism. Arch. Gen. Psychiatr. 59 (9), 809–816. https://doi.org/ 10.1001/archpsyc.59.9.809.
Klin, A., Lin, D.J., Gorrindo, P., Ramsay, G., Jones, W., 2009. Two-year-olds with autism orient to non-social contingencies rather than biological motion. Nature 459 (7244),
257. https://doi.org/10.1038/nature07868.
Kou, J., Le, J., Fu, M., Lan, C., Chen, Z., Li, Q., Zhao, W., Xu, L., Becker, B., Kendrick, K. M., 2019. Comparison of three different eye-tracking tasks for distinguishing autistic from typically developing children and autistic symptom severity. Autism Res. 12 (10), 1529–1540. https://doi.org/10.1002/aur.2174.
Kwon, M.-K., Moore, A., Barnes, C.C., Cha, D., Pierce, K., 2019. Typical levels of eye-region fixation in toddlers with autism spectrum disorder across multiple contexts. J. Am. Acad. Child Adolesc. Psychiatr. 58 (10), 1004–1015. https://doi.org/10.1016/j.jaac.2018.12.011.
Landry, R., Bryson, S.E., 2004. Impaired disengagement of attention in young children with autism. JCPP (J. Child Psychol. Psychiatry) 45 (6), 1115–1122. https://doi.org/ 10.1111/j.1469-7610.2004.00304.x.
Lord, C., Rutter, M., DiLavore, P.C., Risi, S., Gotham, K., Bishop, S.L., 2012. Autism Diagnostic Observation Schedule, second ed. Western Psychological Services. *(AD5S-27*.
Masedu, F., Vagnetti, R., Pino, M.C., Valenti, M., Mazza, M., 2021. Comparison of visual fixation trajectories in toddlers with autism spectrum disorder and typical development: a Markov chain model. Brain Sci. 12 (1), 10. https://doi.org/10.3390/brainsci12010010.
Mullen, E.M., 1995. Mullen Scales of Early Learning. AGS ed.
Norbury, C.F., Brock, J., Cragg, L., Einav, S., Griffiths, H., Nation, K., 2009. Eye-movement patterns are associated with communicative competence in autisticspectrum disorders. JCPP (J. Child Psychol. Psychiatry) 50 (7), 834–842. https:// doi.org/10.1111/j.1469-7610.2009.02073.x.
Ozonoff, S., Young, G.S., Carter, A., Messinger, D., Yirmiya, N., Zwaigenbaum, L., Bryson, S., Carver, L.J., Constantino, J.N., Dobkins, K., Hutman, T., Iverson,

e488–e495. https://doi.org/10.1542/peds.2010-2825.
Pierce, K., Conant, D., Hazin, R., Stoner, R., Desmond, J., 2011. Preference for

geometric patterns early in life as a risk factor for autism. Arch. Gen. Psychiatr. 68 (1), 101–109. https://doi.org/10.1001/archgenpsychiatry.2010.113.
Pierce, K., Marinero, S., Hazin, R., McKenna, B., Barnes, C.C., Malige, A., 2016. Eye-tracking reveals abnormal visual preference for geometric images as an early biomarker of an ASD subtype Associated with increased symptom severity. Biol. Psychiatr. 79 (8), 657–666. https://doi.org/10.1016/j.biopsych.2015.03.032.
Pino, M.C., Vagnetti, R., Valenti, M., Mazza, M., 2021. Comparing virtual vs real faces expressing emotions in children with autism: an eye-tracking study. Educ. Inf. Technol. 26 (5), 5717–5732. https://doi.org/10.1007/s10639-021-10552-w.
Riby, D., Hancock, P.J.B., 2009. Looking at movies and cartoons: eye-tracking evidence from Williams syndrome and autism. J. Intellect. Disabil. Res.: JIDR 53 (2), 169–181. https://doi.org/10.1111/j.1365-2788.2008.01142.x.
Robain, F., Franchini, M., Kojovic, N., Wood de Wilde, H., Schaer, M., 2020. Predictors of treatment outcome in preschoolers with autism spectrum disorder: an observational study in the greater Geneva area, Switzerland. J. Autism Dev. Disord. https://doi. org/10.1007/s10803-020-04430-6.
Rogers, S.J., Vismara, L., Wagner, A.L., McCormick, C., Young, G., Ozonoff, S., 2014. Autism treatment in the first year of life: a pilot study of infant start, a parent-implemented intervention for symptomatic infants. J. Autism Dev. Disord. 44 (12), 2981–2995. https://doi.org/10.1007/s10803-014-2202-y.
Rosset, D.B., Santos, A., Da Fonseca, D., Poinso, F., O'Connor, K., Deruelle, C., 2010. Do children perceive features of real and cartoon faces in the same way? Evidence from typical development and autism. J. Clin. Exp. Neuropsychol. 32 (2), 212–218. https://doi.org/10.1080/13803390902971123.
Sacrey, L.-A.R., Armstrong, V.L., Bryson, S.E., Zwaigenbaum, L., 2014. Impairments to visual disengagement in autism spectrum disorder: a review of experimental studies from infancy to adulthood. Neurosci. Biobehav. Rev. 47, 559–577. https://doi.org/ 10.1016/j.neubiorev.2014.10.011.
Sacrey, L.-A.R., Bryson, S.E., Zwaigenbaum, L., 2013. Prospective examination of visual attention during play in infants at high-risk for autism spectrum disorder: a longitudinal study from 6 to 36 months of age. Behav. Brain Res. 256, 441–450. https://doi.org/10.1016/j.bbr.2013.08.028.
Saitovitch, A., Bargiacchi, A., Chabane, N., Phillipe, A., Brunelle, F., Boddaert, N., Samson, Y., Zilbovicius, M., 2013. Studying gaze abnormalities in autism: which type of stimulus to use? Open J. Psychiatr. 3 (2), 32–38. https://doi.org/10.4236/ojpsych.2013.32A006.
Sparrow, S.S., Balla, D.A., Cicchetti, D.V., 2005. Vineland II: Vineland Adaptive Behavior Scales. American Guidance Service.
Sperdin, H.F., Coito, A., Kojovic, N., Rihs, T.A., Jan, R.K., Franchini, M., Plomp, G., Vulliemoz, S., Eliez, S., Michel, C.M., Schaer, M., 2018. Early alterations of social brain networks in young children with autism. Elife 7, e31670. https://doi.org/10.7554/eLife.31670.
Strobl, M.A.R., Lipsmeier, F., Demenescu, L.R., Gossens, C., Lindemann, M., De Vos, M., 2019. Look me in the eye: evaluating the accuracy of smartphone-based eye tracking for potential application in autism spectrum disorder research. Biomed. Eng. Online 18 (1). https://doi.org/10.1186/s12938-019-0670-1.
Todorova, G.K., Hatton, R.E.M., Pollick, F.E., 2019. Biological motion perception in autism spectrum disorder: a meta-analysis. Mol. Autism. 10, 49. https://doi.org/ 10.1186/s13229-019-0299-8.
Unruh, K.E., Sasson, N.J., Shafer, R.L., Whitten, A., Miller, S.J., Turner-Brown, L., Bodfish, J.W., 2016. Social orienting and attention is influenced by the presence of competing nonsocial information in adolescents with autism. Front. Neurosci. 10, 586. https://doi.org/10.3389/fnins.2016.00586.
van der Geest, J.N., Kemner, C., Camfferman, G., Verbaten, M.N., van Engeland, H., 2002. Looking at images with human figures: comparison between autistic and normal children. J. Autism Dev. Disord. 32 (2), 69–75. https://doi.org/10.1023/a:1014832420206.
van 't Hof, M., Tisseur, C., van Berckelear-Onnes, I., van Nieuwenhuyzen, A., Daniels, A. M., Deen, M., Hoek, H.W., Ester, W.A., 2021. Age at autism spectrum disorder diagnosis: a systematic review and meta-analysis from 2012 to 2019. Autism 25 (4), 862–873. https://doi.org/10.1177/1362361320971107.
Wang, Q., Hu, Y., Shi, D., Zhang, Y., Zou, X., Li, S., Fang, F., Yi, L., 2018. Children with autism spectrum disorder prefer looking at repetitive movements in a preferential looking paradigm. J. Autism Dev. Disord. 48 (8), 2821–2831. https://doi.org/10.1007/s10803-018-3546-5.
Whitehouse, A.J.O., Varcin, K.J., Pillar, S., Billingham, W., Alvares, G.A., Barbaro, J., Bent, C.A., Blenkley, D., Boutrus, M., Chee, A., Chetcuti, L., Clark, A., Davidson, E., Dimov, S., Dissanayake, C., Doyle, J., Grant, M., Green, C.C., Harrap, M., et al., 2021. Effect of preemptive intervention on developmental outcomes among infants showing early signs of autism: a randomized clinical trial of outcomes to diagnosis. JAMA Pediatr., e213298 https://doi.org/10.1001/jamapediatrics.2021.3298.
Zwaigenbaum, L., Bryson, S., Rogers, T., Roberts, W., Brian, J., Szatmari, P., 2005. Behavioral manifestations of autism in the first year of life. Int. J. Dev. Neurosci. 23 (2–3), 143–152. https://doi.org/10.1016/j.ijdevneu.2004.05.001.

## 6.5 Manuscript in preparation: Study 5

# Measuring the impact of face levels of realism on visual exploration of children with Autism Spectrum Disorder

Robain F. Godel M., Franchini M., Schaer M. (in prep.)

## Introduction

In the modern era, the prevalence of avatars, human-like characters, and early exposure to screens for children is increasing (Dong et al., 2021; Slobodin et al., 2019) despite recommendations to avoid screen during early infancy (World Health Organization, 2019). In addition, the line between reality and virtual is becoming increasingly blurred due to the rapid evolution of virtual reality (VR), augmented reality (AR) and extended reality (XR) technologies. Add to this the growing interest in the metaverse and the conception of reality as we knew it needs to be reconsidered (Cerasa et al., 2022). Although these changes are perceived as progress and offer many opportunities in many fields, some may question the impact of all these immersive technologies blurring the border between virtual and reality. We can notably question the consequences that this might have on people with inherent difficulties with humans and social relationships as it is for individuals with autism. Indeed, the literature is extensive on the difficulties of people with autism regarding their social difficulties and these are at the very heart of the diagnostic criteria of this neurodevelopmental disorder (American Psychiatric Association, 2013). Numerous eye-tracking studies have shown an atypical visual exploration of social stimuli in people with ASD (Guillon et al., 2014; Klin et al., 2009; Pierce et al., 2011). The latter is perceived by some frameworks as the cause of their symptoms through a complex developmental cascade (Chevallier et al., 2012). Some researchers have attempted to use the advances in our technologies to provide innovative interventions for the social skills of individuals with ASD. For instance, virtual reality tools have been developed for children therapy, including those with ASD, as documented in a review by Mesa-Gresa et al. (2018). Currently, avatars are the preferred representation of humans or social beings within these therapies due to their ease of customization and creation.

Yet, the impact of realism on visual exploration of social stimuli has been scarcely studied in ASD and multiple types of stimuli are used and considered equivalent despite not being a real human. In other words, it may be urgent to question whether it is relevant to use avatars in studies aiming at improving face recognition if the latter are not explored in the same way as real faces?  What we currently know from recent meta-analyses is that social information processing in individuals with ASD may not affected by the low ecological validity and complexity (Chita-Tegmark, 2016). However, the use of non-realistic social stimuli in such studies remains limited, and it is unclear whether individuals with ASD exhibit atypical visual exploration of social stimuli with different levels of realism (Riby and Hancock, 2009; van der Geest et al., 2002; Atherton and Cross, 2021; Pino et al., 2021; Rosset et al., 2010, Robain et al. 2022). Investigating this effect actual matters for numerous reasons. The first one reason lies in the fact that, if we evidence differences in visual explorations between realistic and non-realistic faces for example, this will considerably increase our knowledge regarding the inherent characteristics that are avoided by people with ASD. Indeed, we could then try to slowly modify it to better understand what is it that causes these differences. It may be that non-realistic faces are more contrasted or just simpler. On the other hand, the absence of differences, resulting in typical visual exploration patterns in non-realistic faces would suggest that research could keep investigating at social orienting or design remediation tool using non-realistic stimuli, which are more tunable. Taken together it is urgent to investigate the impact of the level of realism of social stimuli on the visual exploration of children to better design tomorrow's paradigms and interventions.

During this study, we aim to investigate at the impact of face realism on the visual exploration of both ASD and TD children. We designed a task with a gaze-contingent mask hiding peripheric visual field so that children must explore faces actively. During this task, children were exposed to several faces from 3 categories, the first one being realistic photography of faces, the second one being 3D avatar and the last one being more simplistic cartoon faces. Our first hypothesis is that children with ASD will look at faces in an atypical manner compared to our TDs. Specifically, children with ASD will look at the lower part of the face more than TDs. We also hypothesize that children with ASD will explore the stimuli from all conditions similarly. In contrast, control children should explore faces differently depending on the type of stimulus. In particular, they would be expected to look at avatars differently due to their in-betweenness with real stimuli and the proven "Uncanny valley effect" supposed to develop during early childhood (Feng et al., 2018).

# Method

### *Sample*

Our original sample included 61 recordings. Recordings belonged to children from the Autism Geneva cohort described in previous studies (Franchini et al., 2017; Robain et al., 2020) that aims to longitudinally follow children through their development from 6 months to 12 years of age. A clinical diagnosis in accordance to DSM-5 (American Psychiatric Association, 2013) criteria and a standardized assessment (i.e. Autism Diagnosis Observation Schedule, 2nd edition, ADOS-2, Lord et al., 2012) were used to confirm the diagnosis of children with autism. Out of the 61 initial recordings, we excluded 20 recordings of children who did not watch the task for at least 50% of the time to ensure minimal data quality. In addition, from the children included we only considered trials exceeding 50% of screen time during the analyses. The final sample therefore included 30 children with ASD and 11 TD children (see Table 1 for demographics). The investigation was carried out in accordance with Declaration of Helsinki's latest version. Participants' parents gave their written consent in accordance with protocols approved by the institutional review board of the University of Geneva.

**Table 1** - Sample demographics

| | | TD | ASD | *p.* |
|---|---|---|---|---|
| N = 41 | | *n* = 11 | *n* = 30 | |
| **Age** | | 59.56 (±34.51) | 61.77 (±33.81) | .854 |
| **ADOS** | RRB | 1.55 (±1.81) | 8.70 (±1.95) | **<.001** |
| | SA | 1 (±0) | 6.48 (±1.82) | **<.001** |
| | **Total** | 1 (±0) | 7.31 (±1.95) | **<.001** |
| **Vineland** | Communication | 108.10 (±13.13) | 93.74 (±13.90) | **.008** |
| | Daily Living Skills | 105.00 (±11.86) | 88.04 (±12.24) | **.001** |
| | Socialization | 103.10 (±10.85) | 86.67 (±15.59) | **.005** |
| | Motor skills | 104.67 (±6.98) | 94.24 (±13.13) | **.031** |
| | **Total** | 106.00 (±11.83) | 90.04 (±11.73) | **.001** |
| **Best Estimate IQ** | **Total** | 110.69 (±16.00) | 92.14 (±17.39) | **.004** |

*Task*

Participants sat at approximately 60 cm from the screen. Children who could not stay still sat on their parent's lap when possible. A five-point calibration for toddlers was administered at the beginning of the task and children were then looking freely at the screen. The task was presented on a 1920 × 1200 screen of 24″ and recorded using a TX300 Tobii eye-tracker though Psychtoolbox and Tobii Analytics Software Development Kit for Matlab (2022b for Windows).

The task consisted in a 2-minute gaze-contingent task during which 12 faces were presented during 10s each. A fixation cross was presented during one second between faces. Faces belonged to three different conditions: realistic (see Fig. 1 a), avatar (see Fig. 1 b) or cartoon (see Fig. 1 c). The realistic faces were photographs from the Chicago Face Database, version 3.0 (CFD, Ma et al., 2015). The avatar and cartoon faces were created for the task using CrazyTalk software. Each condition included 4 faces with equal gender repartition.


**Figure 1** - Sample face stimuli by condition **a)** Realistic condition face **b)** Avatar condition face **c)** Cartoon condition face

The task was inspired from a study by Wang et al. (2019) who used a gaze contingent paradigm to reveal a blurred face where the participant was looking at. This paradigm allowed them to investigate whether children with ASD use peripheral vision to process less explored areas of the face (e.g., eye region). Thus, by blocking the latter, it was necessary for the children to direct their gaze towards the areas they considered relevant for the task, without any possibility of peripherally processing them. Similar to Wang et al., we included a gaze contingent mask revealing content according to gaze position. We believe that ensuring that no compensatory mechanisms were possible make the comparison between time spent on the various parts of the face across conditions more insightful compared to an unmasked face viewing task. Yet, faces were presented in a clear way at the beginning of each trial during one second. By doing this clear presentation, our participants were aware of the type of face but did not have enough time to explore it. After this second of clear presentation, faces were covered by our mask which consisted in a gaze contingent aperture of 5° of visual angle through an opaque layer. This aperture size was chosen because it corresponds to the size of the foveal vision within the field of vision and thus excludes the peripheral field of vision. This also allowed only one part of the face to be seen at a time when the mask was applied.

*Eye-tracking measures*

We investigated the visual time repartition on different regions of faces using discrete Areas of Interest (AOIs). We analyzed a total of 4 AOIs, including the Upper (Fig. 2 a) and Lower (Fig 2 c) part of the face as well as subregions AOIs such as Eye (Fig. 2 b) and Mouth (Fig. 2 d) region.

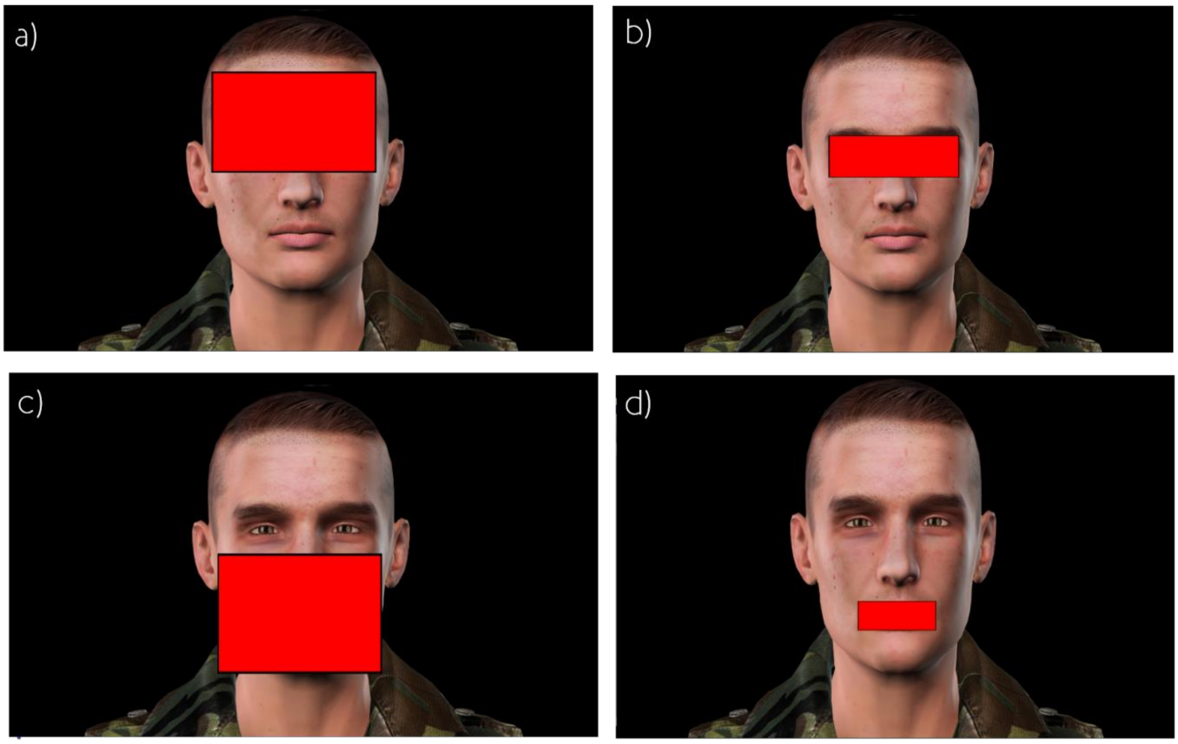



**Figure 2** - Areas of Interest on a male avatar face **a)** AOI for the Upper part of the face **b)** AOI for the Eye subregion **c)** AOI for the Lower part of the face **d)** AOI for the Mouth subregion

From these AOIs, we computed several measures of interest. The main one corresponded to the percentage of time spent on an AOI relative to the total time spent looking at the screen during the trial. Again, these percentages were computed using valid trials only. Trials were considered valid when their watching time was greater than 50% of their total duration. Trials watched less than 50% were therefore discarded and not included in the AOI percentage calculation (e.g., percentage on mouth in the Avatar condition). Finally, we also computed an evolutive percentage of time spent on an AOI according to the time into the trial. By computing this variable across time, we hope to see how the attention of children evolved during the trial. We expect to see a quite coherent and common pattern of exploration across time in the TD group. On the contrary, we expect a more eclectic and random exploration within the ASD group regardless of the condition.

### *Behavioral measures*

To achieve a better understanding of the ASD phenotype, children from our cohort are assessed using multiple behavioral assessments. We used the ADOS-2 calibrated severity scores from (Gotham et al., 2009; Hus et al., 2014) which give Restricted and Repetitive Behaviors (RRB), Social Affect (SA) and Total severity scores to investigate at autism symptom severity. In addition, we used the Vineland Adaptive Behavior Scale, 2nd edition (VABS-II, Sparrow et al., 2005) to assess adaptive skills. Finally, we either took scores from the Mullen Scales of Early Learning (MSEL, Mullen, 1995), Wechsler Preschool and Primary Scale of Intelligence, 4th edition (WPPSI-IV, Wechsler, 2012) or the Wechsler Intelligence Scale for Children, 5th edition (WISC-V, Wechsler, 2014), according to the level and age of the participant. In order not to split our sample into subsamples, we merged these tests in a Best Estimate IQ, representing the closest estimation of a child's IQ by the time of the assessment.

### *Analyses*

Analyses were conducted using IBM SPSS Statistics for MacIntosh, Version 24.0 (Armonk, NY: IBM Corp.), and plotted using GraphPad Prism 9 (GraphPad Software, La Jolla California USA, www.graphpad.com). We plotted heatmaps (see Annex – Fig.1) using iMap4 (Lao et al., 2017). As for the statistical analyses, we first performed ANOVA to compare all variables. We then used repeated measures general linear model to investigate the effect of condition within our whole sample. We repeated these analyses within each group to explore specific effects within each of them. We performed GLM analyses on the evolutive percentage over time on the AOIs where we identified significant differences. Finally, we used correlations to investigate the relationship between behavioral and eye-tracking measures within the ASD group only.

## Results

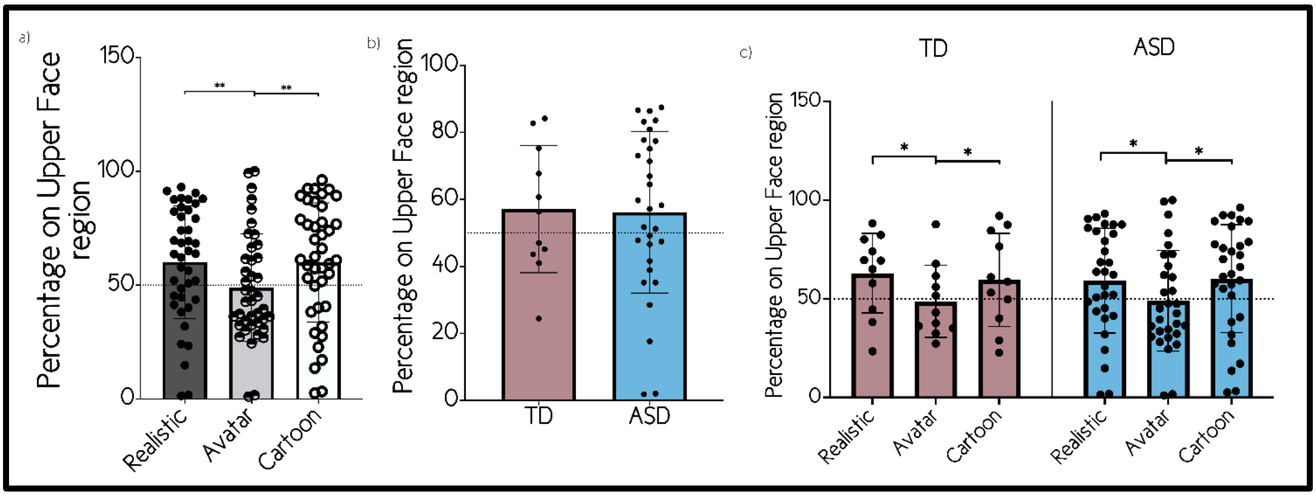



**Figure 3** - Percentage of time spent on Upper Face region **a)** Percentage on the Upper Face region by condition **b)** Percentage on the Upper Face region by group **c)** Percentage on the Upper Face region by group*condition

Upper face AOI (see Fig. 3): The results of our repeated measures GLM indicated a significant main effect of Condition ($F(2, 78) = 8.824$, $p < .001$, $\eta^2 = .966$) on the percentage of time spent on the upper face region, suggesting that participants' gaze patterns varied across different conditions. However, the interaction between Condition and Group was not significant $F(2, 78) = .299$, $p > .05$, $\eta^2 = .096$, indicating that the effect of Condition on the percentage of time spent on upper part of the face was consistent across different groups. Condition-wise, post-hoc pairwise comparisons indicated that there was a significant mean difference of -11.002 (SE = 3.406, $p = .008$). Participants spent significantly less time looking at the upper part of the face in the Avatar condition compared to Cartoon condition. Similarly, there was a significant mean difference of -12.189 (SE = 3.529, $p = .004$) in the Avatar condition compared to the Realistic condition. The mean difference of -1.186 (SE = 2.581, $p > .05$) between Cartoon and Realistic was not significant. In summary, the post-hoc analyses revealed that participants spent significantly less time looking at the eye region in the Avatar condition compared to both the Cartoon and Realistic conditions. However, there was no significant difference between the Cartoon and Realistic conditions. We finally analyzed differences between groups in all 3 conditions. In the avatar condition, no significant difference was found between groups (B = -.235, SE = 8.409, $t(39) = -.028$, $p > .05$). Regarding the cartoon condition, no significant difference was found between groups (B = -.695, SE = 9.329, $t(39) = -.075$, $p > .05$). Regarding the realistic condition, no significant difference was found between groups (B = 3.804, SE = 8.822, $t(39) = .431$, $p > .05$). Within-group comparison using paired t-tests showed significant differences in the time spent on the upper face region between Avatar and Cartoon conditions ($t(10) = 2.801$, $p < .05$) and between Realistic and Avatar conditions ($t(10) = 3.057$, $p < .05$) within the TD group. However, no significant difference was found between Cartoon and Realistic conditions ($t(10) = -0.715$, $p > .05$) for the same group. Similarly, in the ASD group, significant differences were observed between Avatar and Cartoon conditions ($t(29) = 2.913$, $p < .05$) and between Realistic and Avatar conditions ($t(29) = 2.605$, $p < .05$), while no significant difference was found between Cartoon and Realistic conditions ($t(29) = 0.411$, $p > .05$) regarding the time spent on the upper face region.

Eye AOI: The results of our repeated measures GLM indicated a significant main effect of Condition (F(2, 78) = 9.762, $p$ < .001, $\eta^2$ = .979) on the percentage of time spent on the eye region, suggesting that participants' gaze patterns varied across different conditions. However, the interaction between Condition and Group was not significant (F(2, 78) = 1.121, $p$ > .05, $\eta^2$ = .241), indicating that the effect of Condition on the percentage of time spent on the eye region was consistent across different groups. Condition-wise, post-hoc pairwise comparisons indicated that there was a significant mean difference of -13.231 (SE = 3.503, $p$ = .002). Participants spent significantly less time looking at the eye region in the Avatar condition compared to the Cartoon condition. There was a significant mean difference of -12.527 (SE = 3.629, $p$ = .004). Participants spent significantly less time looking at the eye region in the Avatar condition compared to the Realistic condition. The mean difference of 0.704 (SE = 2.936, $p$ = 1.000) was not significant. There was no significant difference in the percentage of time spent on the eye region between the Cartoon and Realistic conditions. In summary, the post-hoc analyses revealed that participants spent significantly less time looking at the eye region in the Avatar condition compared to both the Cartoon and Realistic conditions. However, there was no significant difference between the Cartoon and Realistic conditions. We finally analyzed differences between groups in all 3 conditions. In the avatar condition, no significant difference was found between groups (B = 4.028, SE = 7.605, t(39) = .530, $p$ > .05). Regarding the cartoon condition, no significant difference was found between groups (B = 0.759, SE = 9.944, t(39) = .076, $p$ > .05). Regarding the realistic condition, no significant difference was found between groups (B = 10.659, SE = 8.870, t(39) = 1.202, $p$ > .05). Within-group comparison using paired t-tests showed significant differences in the time spent on the eye region between Avatar and Cartoon conditions (t(10) = 3.195, $p$ < .05) and between Realistic and Avatar conditions (t(10) = 3.478, $p$ < .05) within the TD group. However, no significant difference was found between Cartoon and Realistic conditions (t(10) = -0.824, $p$ > .05) for the same group. Similarly, in the ASD group, significant differences were observed between Avatar and Cartoon conditions (t(29) = 3.711, $p$ < .05) and between Realistic and Avatar conditions (t(29) = 2.276, $p$ < .05), while no significant difference was found between Cartoon and Realistic conditions (t(29) = 1.876, $p$ > .05) regarding the time spent on the eye region.

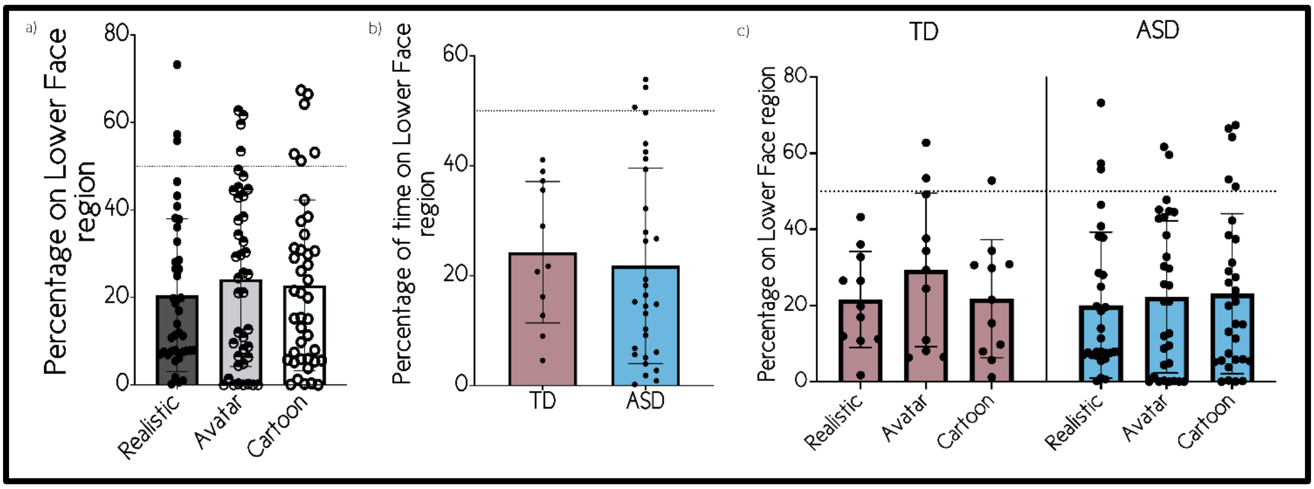



**Figure 4** - Percentage of time spent on Lower Face region **a)** Percentage on the Lower Face region by condition **b)** Percentage on the Lower Face region by group **c)** Percentage on the Lower Face region

by group*condition

Lower part AOI (see Fig. 4): The results of our repeated measures GLM indicated an absence of significant effect regarding Condition ($F(2, 78) = 1.518$, $p = > .05$, $\eta^2 = 3.036$) and the Condition*Group interaction ($F(2, 78) = 1.084$, $p = >. 05$, $\eta^2 = 2.168$). Between groups analyses on all 3 conditions evidenced no significant between groups differences in the avatar (B = 7.097, SE = 7.050, t(39) = 1.007, $p > .05$), cartoon (B = -1.315, SE = 6.963, t(39) = -.189, $p > .05$) and realistic conditions (B = 1.486, SE = 6.247, t(39) = .238, $p > .05$). Within group comparison using paired t-tests showed no significant difference between Avatar and Cartoon (t(10) = -1.419, $p > .05$), Cartoon and Realistic (t(10) = 0.047, $p > .05$) and Realistic and Avatar conditions (t(10) = -1.368, $p > .05$) within the TD group. Similarly, no differences where found in the ASD group, regarding their time spent on the lower face region between Avatar and Cartoon conditions (t(29) = 0.295, $p > .05$), Cartoon and Realistic conditions (t(29) = 1.291, $p > .05$) and Realistic and Avatar conditions (t(29) = -0.626, $p > .05$).

Mouth AOI: The results of our repeated measures GLM indicated an absence of significant effect regarding Condition ($F(2, 78) = .927$, $p = > .05$, $\eta^2 = 1.855$) and the Condition*Group interaction ($F(2, 78) = 1.223$, $p = > .05$, $\eta^2 = 2.446$). Between groups analyses in all 3 conditions evidenced no significant between groups differences in avatar condition (B = -.322, SE = 2.263, t(39) = -.142, $p > .05$) cartoon(B = 2.349, SE = 1.785, t(39) = 1.316, $p > .05$) nor the realistic condition (B = .011, SE = 1.659, t(39) = .007, $p > .05$). Within-group comparison using paired t-tests revealed no significant differences in the time spent on the mouth region between Avatar and Cartoon conditions (t(10) = 0.620, $p > .05$), Avatar and Realistic conditions (t(10) = 0.984, $p > .05$), and Realistic and Cartoon conditions (t(10) = -1.260, $p > .05$) within the TD group. Similarly, in the ASD group, no significant differences were found between Avatar and Cartoon conditions (t(29) = -1.577, $p > .05$), Avatar and Realistic conditions (t(29) = 1.247, $p > .05$), and Realistic and Cartoon conditions (t(29) = 0.225, $p > .05$) regarding the time spent on the mouth region.

*Temporal dynamic analyses*

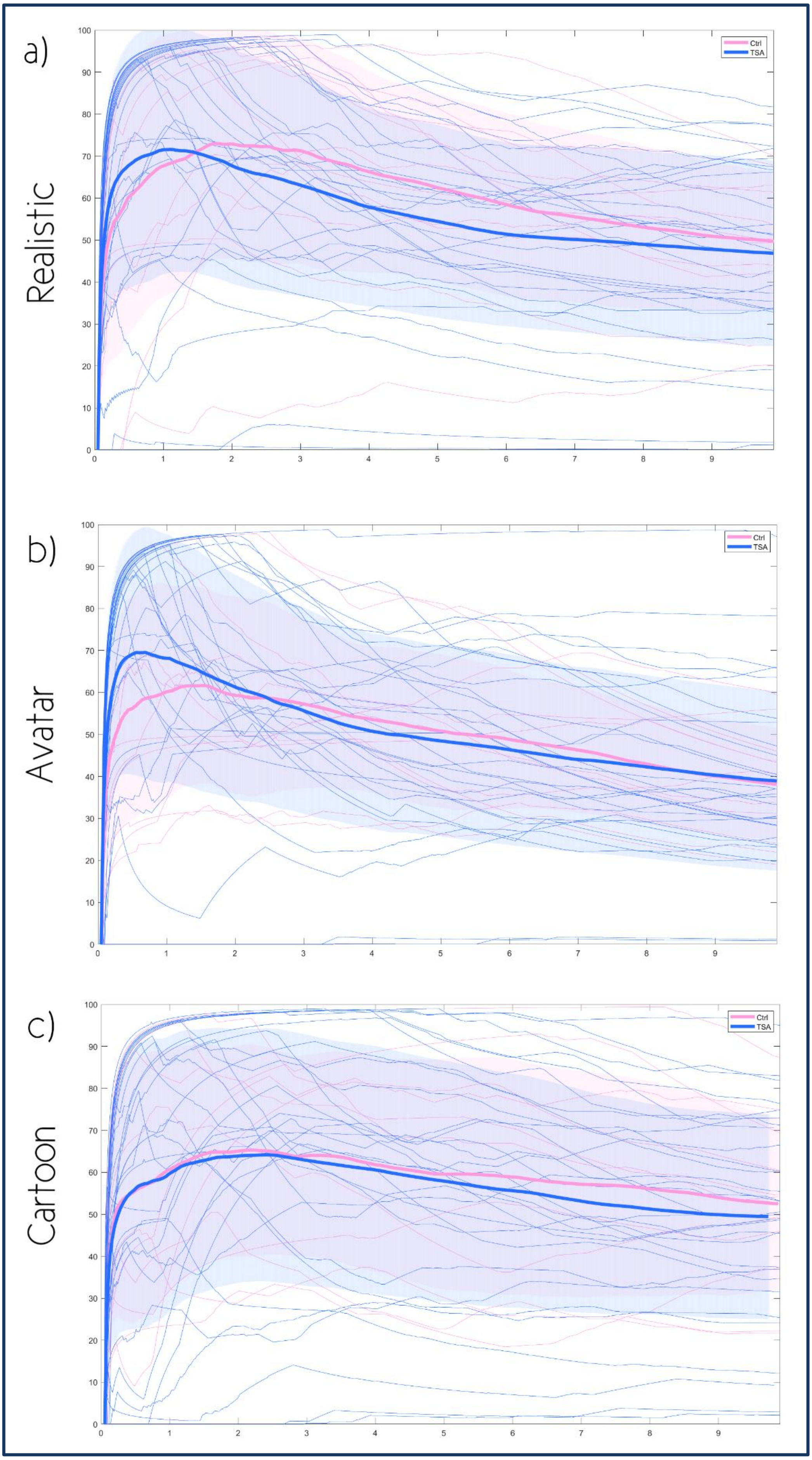

a)
Realistic
Ctrl
TSA
b)
Avatar
Ctrl
TSA
c)
Cartoon
Ctrl
TSA

**Figure 5 -** Mean percentage of time spent on the Upper face region over time per group and condition **a)** Mean evolutive percentage during the Realistic condition **b**) Mean evolutive percentage during the Avatar condition **c)** Mean evolutive percentage during the Cartoon condition

Realistic (see Fig. 5 a) : Our analyses revealed significant effects of time (Estimate = -2.34, SE = 0.32629, t(23916) = -7.1716, *p* < 0.001) suggests that, overall, the percentage the upper face region decreases as time progresses; and a significant interaction between group and time (Estimate = 0.65403, SE = 0.065429, t(23916) = 9.9961, *p* < 0.001) showing that the rate of decrease in the percentage of time on the upper face region is smaller for the TD group compared to the TSA group. In other words, while the percentage of time decreases over time for both groups, the decrease is less pronounced for the TD group than for the ASD group.

Avatar (see Fig 5. b): The linear mixed-effects model revealed significant main effects of time (Estimate = -89.795, SE = 12.733, t(22202) = -7.0522, *p* < 0.001), suggesting a significant decrease of time spent on the upper face region over time ; and a significant group-by-time interaction (Estimate = 60.044, SE = 1.7132, t(22202) = 35.048, *p* < 0.001) evidencing that the rate of change in the percentage of time spent on the upper face region over time is slower in the TD group than in the ASD group. This indicates that the ASD group's percentage decreases more quickly than the TD group's percentage, resulting in a narrowing of the difference between the groups as time progresses.

Cartoons (see Fig. 5 c): The linear mixed-effects time (Estimate = -0.97634, SE = 0.36332, t(24503) = -2.6873, *p* = 0.0072), suggesting a significant decrease of time spent on the upper face region over time; and a significant group-by-time interaction (Estimate = 0.89176, SE = 0.075991, t(24503) = 11.735, *p* < .001), suggesting that the rate of change in the percentage of time spent on the upper face region over time is slower in the TD group than in the ASD group. This indicates that the ASD group's percentage decreases more quickly than the TD group's percentage.

### *Correlations*

We did not observe any significant correlation between any ADOS symptom severity scores and visual explorations parameters in any condition (all *p* > .05). However, we observed significant negative correlations between time spent on the eye-region in the cartoon (r = -.412, *p* < .05) and in the realistic (r = -241, *p* < .05) conditions with age. Interestingly, we identified a positive relationship between communication skills on the VABS and percentage of time spent on the lower part of the face in the realistic condition (r = .445, *p* < .05). Finally, we also identified negative correlations between the total number of fixations and the percentage of time spent on the upper part and eye region in every condition (all *p* < .001).

## Discussion

Our observations indicated that children from both the ASD and TD groups exhibited similar levels of attention towards various Areas of Interest (AOIs) across all conditions. Contrary to the frequently reported decrease in attention to the eyes in ASD children within existing literature (Frazier et al., 2017; W. Jones & Klin, 2013; Klin et al., 2002; Pelphrey et al., 2002). Our findings were not as consistent but yet align with a list of studies (Guillon et al., 2014; van der Geest et al., 2002) that do not reported atypical eye exploration in ASD too. Considering that dynamic and socially interactive environments tend to elicit atypical visual exploration in individuals with ASD (Chevallier, Parish-Morris, et al., 2015; Robain et al., 2021), the relatively simple task that we presented consisting of observing full-screen, static faces might not have been sufficient to reveal differences in visual exploration between the groups. Another potential explanation for the lack of observed differences between the ASD and control groups could be that the mask applied to the faces stimulated exploration in all children, thereby masking the atypical exploration patterns in ASD. However, this hypothesis appears unlikely given the findings of a similar study by Wang et al., (2019). In their study, which presented faces in both "clear" and contingently masked conditions, differences in time spent on the eyes between the groups were observed in both conditions. Notably, their study required participants to identify the gender of the person being viewed, whereas our study allowed for free exploration without a specific goal. It is possible that the results from Wang et al.'s study reflect a more goal-oriented visual exploration of faces, with children with ASD relying more on the lower areas of the face rather than the eyes to determine the person's gender. In contrast, free visual exploration may here represent the natural dynamics of face exploration in children with ASD. However, previous research has suggested that the presence or absence of an instruction has little impact on visual exploration of faces (Pelphrey et al., 2002), rendering this hypothesis little likely as well. Thus, it seems that our task does not simply show a difference in face exploration in this specific context where faces are contingently masked.

Conversely, our findings revealed a significant effect of the condition, particularly in the Avatar condition, which appeared to elicit a distinct exploration pattern compared to the other conditions. We observed a reduced percentage of time spent on the upper/eye area in the Avatar condition relative to the Realistic and Cartoon conditions. This decrease in visual exploration of the eyes in the Avatar condition may be associated with the uncanny valley effect discussed previously. The uncanny valley effect posits that characters with realistic human features are explored atypically and are less appealing due to their ambiguous nature. Research has demonstrated that this effect emerges early in development and is sought to be absent in children with ASD (Feng et al., 2018). The absence of the uncanny valley effect in ASD has been attributed to reduced exploration of areas that trigger this effect, such as the eyes. However, our results suggest that this effect may be present in both of our groups, including children with ASD. The presence of such effect might be related to the fact that our children with ASD watch the eye in a typical manner and were therefore sensitive to ambiguity too. This finding implies that the uncanny valley effect may be more pervasive than previously thought, potentially influencing visual exploration patterns in both neurotypical and populations on the spectrum.

Another intriguing observation was that children with ASD who spent more time looking at the mouth in the Realistic and Cartoon conditions demonstrated better communication scores. This finding aligns with the results of (Klin et al., 2002), who also reported a positive correlation between the time spent looking at the mouth, rather than the eyes, and socialization skills as measured by the VABS in children with ASD during an eye-tracking task involving a social interaction scene. Klin et al. (2002) proposed a compensation mechanism hypothesis to explain this observation. It is plausible that children with ASD who focus more on the mouth are able to compensate for their comprehension difficulties by directly observing the source of speech in others. This compensation mechanism appears to be present in our study as well. The fact that older children were more inclined to look at the mouth supports the idea that this compensatory mechanism develops with age. Another noteworthy correlation is the observation that children who looked less at the eyes were more exploratory in their visual behavior. As suggested above, this might be related to the absence of specific instructions in the task. Overall, it is possible that children who explored more, and consequently spent more time looking at mouths instead of fixating on the eyes, are older children who developed compensatory mechanisms over time.

Finally, in all conditions we observed a different time-dependent exploration across groups. Temporal dynamics suggest that children with ASD lose interest more quickly than TD children, resulting in larger differences in time spent at the beginning of stimulus presentation compared to the end. Although this effect is also observed in TD, it is much less pronounced and the decline less abrupt. Overall, this result underscores the importance of considering the dynamic dimension within eye-tracking analyses and highlights the fact that means can quickly camouflage differences in the dynamic of stimulus exploration. Extrapolating this result slightly, we could suggest that it supports social motivation theory (Chevallier et al., 2012). Although it is difficult to say that children with ASD differ in their interest in this task, it appears that children with ASD have less of a desire to maintain this social interest. Thus, it is possible to interpret this atypical visual exploration dynamic in terms of atypical social motivation.

Despite a very limited sample that constrains the interpretation and generalization of our results, they answer our initial question of whether children with ASD and TD look at faces with different levels of realism in the same way. It seems that both children with ASD and TD look at cartoonish and realistic faces the same way. These findings therefore fill in a gap in the existing literature suggesting that the use of cartoonish characters with simplified features may be relevant to remediate social skills in children with ASD since they are viewed in the same manner as realistic faces. On the other hand, it looks like avatars cause an uncanny valley effect in children with ASD, just as they do in TD children. This effect, unforeseen, should be taken into consideration when developing social stimuli using the avatar form. The boundary between realism/cartoon remains to be investigated to better understand how to design stimuli that would help us better understand how people with ASD explore their social environment.

## Annex

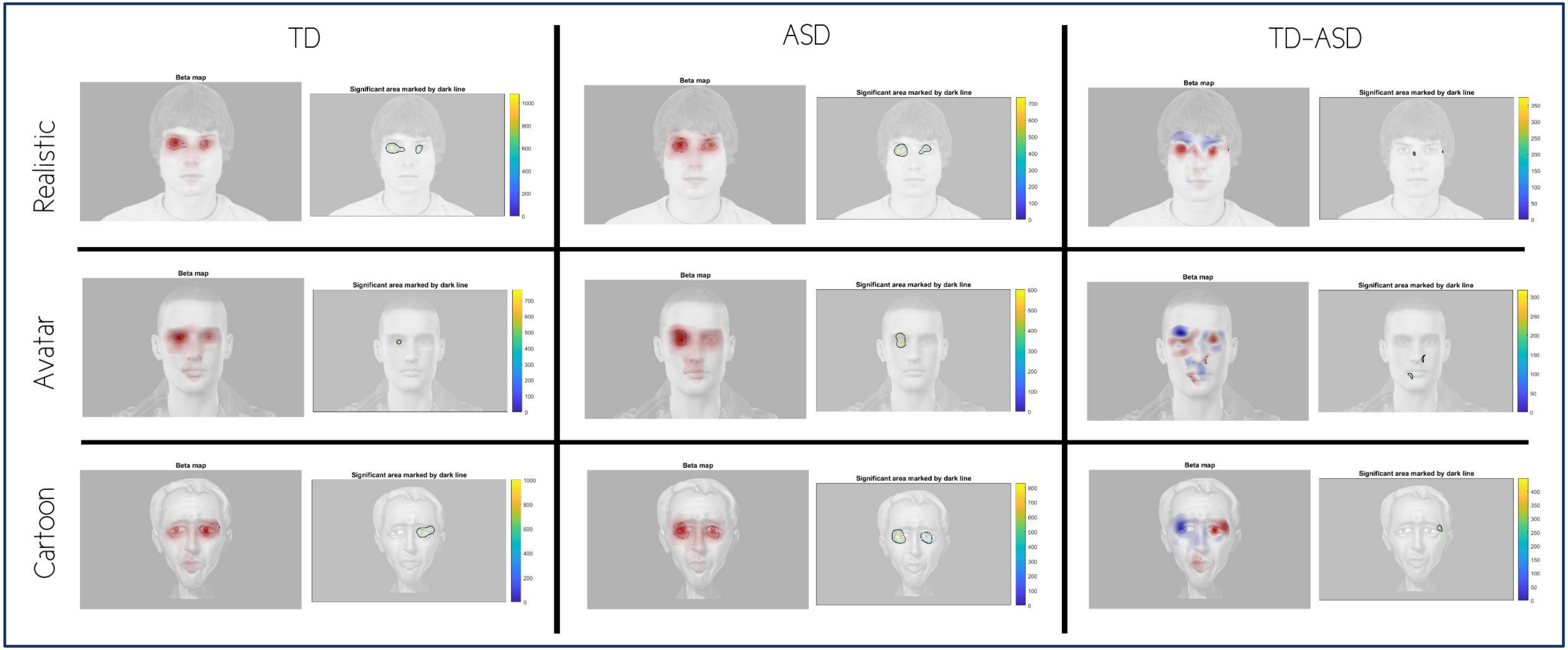



**Figure 1** – Face scanning heatmaps per condition and group, last column represents the difference between groups (TD-ASD)

## 6.6 Manuscript in preparation: Study 6

# Social orienting remediation using eye-tracking in preschoolers with Autism Spectrum Disorder: a randomized controlled trial

Robain F., Godel M., Solazzo S., Latrèche K., Franchini M., Schaer M.

## Introduction

Autism spectrum disorders (ASD) are characterized by delayed language development, social interaction deficits, and the presence of repetitive and stereotyped behaviors (American Psychiatric Association, 2013). Current standards recommend intensive and early intervention for children with ASD. The origin of these disorders remains unknown despite numerous theories. The "social motivation theory" (Chevallier et al., 2012) is among the leading theories, positing a lack of attention to the social environment as the crux of the disorders. According to these authors, social orientation is defined as "the psychological dispositions and biological mechanisms that lead an individual to preferentially orient towards the social world." This theory suggests that ASD arises from a lack of social orientation, which results in fewer social experiences and significantly affects learning, which is highly dependent on observing others during childhood. The accumulation of missed experiences leads to atypical early brain development, reinforced by repeated exposure to non-social stimuli. Many early interventions, such as the Early Start Denver Model (ESDM; Rogers & Dawson, 2010), aim to make interactions and the social world more appealing by using positive reinforcement based on the child's interests. For instance, the sensory-social routines implemented in the ESDM are designed to combine requesting/communicating with the practitioner and receiving enjoyable sensory reinforcement through repeated practice during intervention sessions. Increasing interest in the social world is, therefore, the primary objective of various autism interventions to teach children a range of skills. In line with this approach, the goal of this pilot study is to support an increase in social orientation among young children with autism.

To enhance social orientation, we suggest using eye-tracking, a widely employed tool for quantitatively measuring social orientation (Frazier et al., 2017). This non-invasive tool has a playful aspect generally enjoyed by children. In recent years, eye-tracking studies have diversified, with some proposing a more active and contingent approach to gaze. These studies (Powell et al., 2016; Wang et al., 2020) involve employing gaze to activate stimuli rather than merely recording gaze data. The emergence of these "gaze-contingent" protocols broadens the potential applications of eye-tracking, transitioning it from a measurement tool to a potential remediation instrument. Increasingly, studies propose using this stimulus/looking contingency to address various pathologies, similarly to neurofeedback. The participant's control over on-screen events allows for immediate feedback on the consequences of their visual exploration. For example, a study with anxious patients used a gaze-contingent paradigm to reduce anxiety symptoms (Lazarov et al., 2017 The authors asked participants (40 adult subjects) to select their preferred music, which would act as a positive reinforcer. They then displayed face arrays containing neutral faces and others with negative expressions. The intervention involved playing the preferred music whenever the participant looked at a neutral face. In the control group, music played continuously in the background, with no changes based on gaze direction. The intervention occurred over four weeks with two 20-minute sessions per week. Participants in the gaze-contingent condition experienced a significant increase in time spent looking at neutral faces throughout the sessions, and their anxiety symptoms decreased accordingly. In contrast, the control group showed no symptom improvement, and the time spent gazing at neutral and emotional faces remained unchanged during the sessions. This experiment demonstrates the therapeutic potential of gaze-contingency paradigms in eye-tracking. Initial studies exploring the potential application of these paradigms in children with autism have recently been published, focusing on attentional skills in children with an average age of six years (Powell et al., 2016). A recent study established feasibility in three-year-old children (Wang et al., 2020). Additionally, one study reported that children as young as six months can fully comprehend and respond to gaze-contingent paradigms (Keemink et al., 2019). Collectively, these studies and the remediation potential of eye-tracking inspired us to develop an intervention for young children (under five years old). The primary concept of our project is to propose a gaze-contingent eye-tracking intervention that encourages children to look at social stimuli, which will be positively reinforced upon being viewed, as opposed to non-social stimuli that are not reinforced. As in the aforementioned studies, we hypothesize that children receiving this intervention will progressively increase the time spent looking at social stimuli. The potential to enhance social orientation in young children with autism could ultimately serve as a supplement to early behavioral interventions and thereby act as a positive mediator in response to the intervention.

## Method

### *Design*

The pilot study was monocentric, randomized and controlled. The randomization was done in an automatic way via a homemade Matlab script allowing to randomly assign a participant to a group. The examiner delivering the intervention, the participants (including parents) and the person in charge of the study have been kept uninformed about the group of each participant. The parents of the participants were not informed of exactly how the intervention worked and completed the questionnaires without bias. Indeed, the parents were informed of the general principle of the study, notably the repeated presentation of positive social stimuli to their child using eye-tracking, but the gaze-contingency principle was deliberately concealed during the presentation of the study.

Regarding the timeline of the study (see Fig.1), the intervention took place over 6 sessions of approximately 30 minutes spread over a month. During the first and last session, the questionnaires and eye-tracking tasks were administered as the baseline/outcome measures of the intervention's effects.

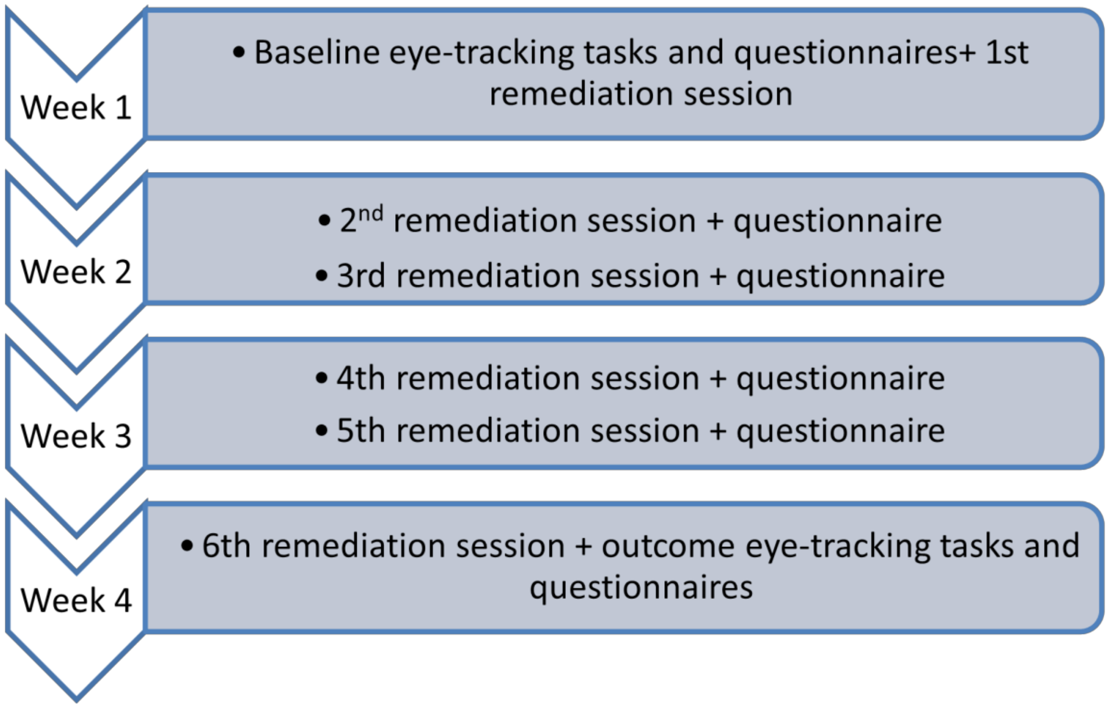



**Figure 1 -** Graphic representation of the timeline of the RCT

*Sample*

This pilot study focused on young children with ASD aged 1.5 to 5 years. Participants in the intervention and control groups shared the same inclusion and exclusion criteria. The recruitment was done through the professionals of the Centre de Consultation Spécialisé en Autisme (CCSA) of Geneva. The latter generally complete diagnostic and developmental assessments as part of their clinical practice. Once it was established that a child met the inclusion criteria for the study, the parents were asked to contact the study investigator if they wanted to be part of if.

As for inclusion criteria, only males were invited to participate for several reasons. The first is that ASD are disorders that affect 4 times more boys than girls (Maenner, 2023). Therefore, it was possible that over the course of the study, only a few girls were diagnosed and might have been difficult to balance the groups, even if we only tried to respect the 4:1 representation generally observed. The second is that autism in girls presents differently (Frazier et al., 2014). Indeed, the literature regarding the female profile in autism is extensive and suggests a more social autism compared to boys. Eye-tracking studies, with tasks similar to ours, suggest attention to social stimuli equivalent to control children in girls with autism while their male peers show diminished social orientation (Harrop et al., 2019). Given the major differences between male and female phenotypes, as well as the small sample size targeted, we therefore excluded girls from this pilot study. The remaining inclusion criteria consisted of being between 1.5 and 5 years of age, having no current intensive intervention, and speaking English or French as their mother tongue. Additional exclusion criteria included the presence of identified genetic or physical comorbidities and attention time to screens under five minutes.

The intervention and control groups will include 20 participants each. At the time of writing, 7 of the

40 planned participants have completed the protocol.

*Eye tracking tasks*

All tasks were coded using Tobii SDK and Matlab (MacOs v.2020b). Tasks were displayed on a 24'' 1920x1080 screen and gaze data recorded through a TX300 eye-tracker. Regarding assessment procedure, participants sat approximately 60cm away from the screen and were asked to stay as still as they could. If a participant was unable to stay still, parents were invited to join so that their child could sit on their lap.

Task 1 (see Fig.2): This first task was inspired by Lazarov et al. (2017) who used a similar design to decrease symptoms of patients with anxiety disorders. This task displayed a total of 26 arrays of 12 images for 10 seconds each. A centering circle was presented for 1 second between stimuli. The 12 images from each array were split in 2 categories each subdivided in 2 subcategories: Social images divided in happy (HF) and neutral faces (NF); Non-social images divided in high interest for ASD images (HIA) and low interest for ASD images (LIA).
Social images were extracted from the Chicago face database (CFD, Ma et al., 2015) allowing the use of standardized faces of males and females varying in age, emotion, and ethnicity. From this database, we selected 80 happy faces and 80 neutral faces ensuring that there was an equivalent 1:1 gender distribution. Among these 160 images, we selected several ethnic groups with different distributions according to their representation in Europe. We therefore included 41.25% (66 images) of white Caucasian, 41,25% (66 images) of African faces, 17.5% (28 images) of minor ethnic groups (e.g. Indians, Hispanics). Each final array contained 3 happy faces, 3 neutral being 3 males and 3 females as well as a minimum of 2 African and 2 white Caucasian and a minimum of 1 minor ethnicity among each.
Non-social images were extracted from the Bank of Standardized Stimuli (BOSS; Brodeur et al, 2014) allowing the use of normalized images belonging to well defined categories. High and Low interest images categories were the ones suggested by Sasson (2012) and Chevallier (2015) namely: trains, vehicles, planes, electronic devices, and road signs for HIA and clothing, furniture, plants, hats, bags, school supplies for the LIA. Each final array included 3 HIA and 3 LIA. All arrays were presented in the same order for every child of both groups. All AOIs were of 480x360 pixels to fit the overall 1920x1080 display screen. Regarding measures, we recorded time to first fixation on a face, difference in speed to look at a face between trials, total time spent on the screen, percentage of time spent on faces, objects, males/females, happy/neutral faces, and finally HIA/LIA.

For the remediation group, social images were contingent and gazing at them was positively reinforced by playing a free of rights child-friendly music. Music was a new one for each array and therefore 26 short music were played. Non-social images were non-contingent and therefore not reinforced.
For the control group, a list of timepoint and associated duration between 1 and 3 seconds were randomly generated before the study. Music was triggered when the timepoints were reached for the associated duration. This allowed us to trigger music on a random basis while controlling for the timing and duration within the control group by experiencing the same amount of auditive stimulation at the

exact same timing but changing from one session to another to avoid anticipation.

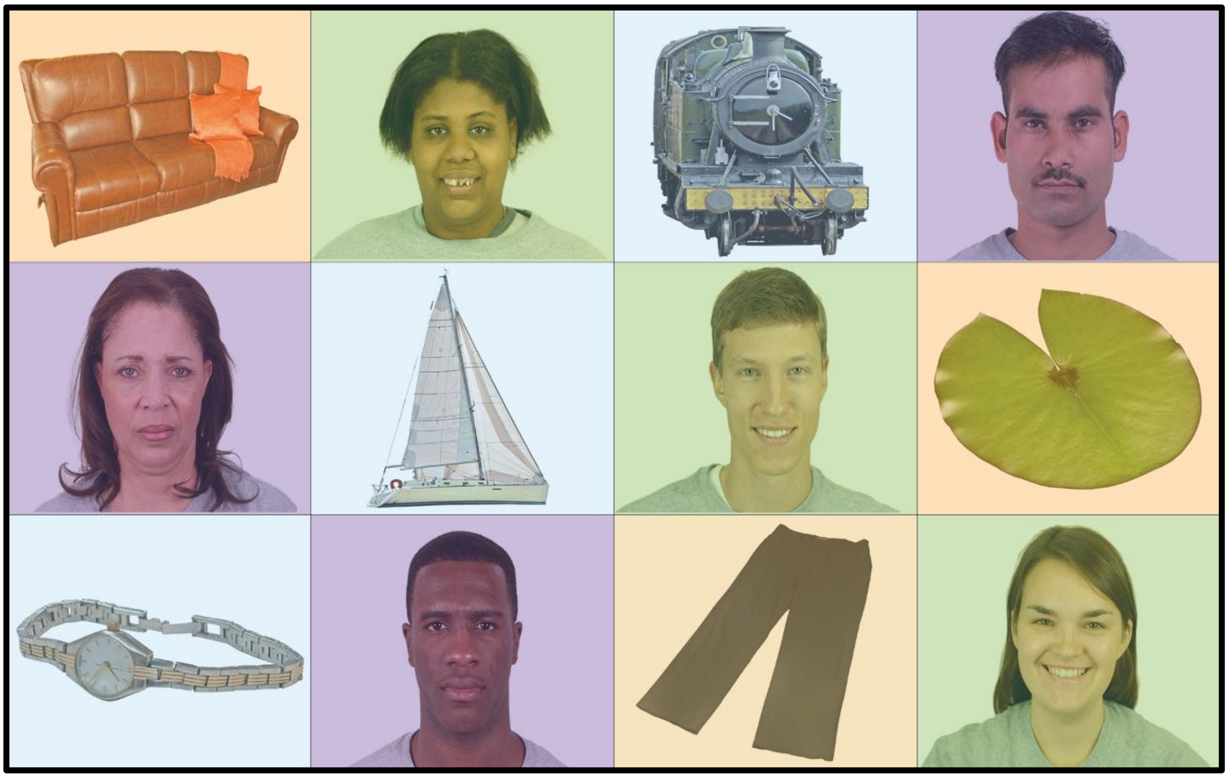


Figure 2 - Example array of images with colorized AOIs for each category. Green AOIs correspond to Happy faces (HF) images, purple AOIs correspond to Neutral faces (NF), blue AOIs correspond to High interest for autism images (HIA) and orange AOIs correspond to Low interest images for autism (LIA).

Task 2 (see Fig.3): In the second task, the child was asked to watch a cartoon with a virtual avatar. The screen was divided into 3/4 for the cartoon and 1/4 for the avatar. Pauses were integrated during the task, during which the avatar was no longer looking at the cartoon but at the child. The gaze-contingency intervened during these pauses, as it was possible to look at the avatar's face to instantly resume the cartoon. Otherwise, it was automatically restarted after a 5 second delay. In the control group, the pauses were not gaze-contingent and only ended after 5 seconds, plus a random duration between 1-3 seconds to avoid implicit duration learning.

The cartoon used in this task is the Penguins cartoon from the Animanimals series. We chose this cartoon featuring a penguin banquet, as it is relatively simple to understand and does not contain any language, therefore avoiding any bias.

The avatar on the right side of the screen was created for the study via the CrazyTalk software. The avatar spoke directly to the child to explain that they were going to watch a cartoon, to announce the end of each pause or to announce the end of the session and invite him for a next one. When the cartoon was playing, the avatar looked in its direction and reacted to its sounds by moving a bit, blinking, and smiling. As the pauses approached, the avatar gradually turned to face the child until it was completely in front of him with a neutral expression, therefore prompting the pauses. When reactivated, the avatar announced that the cartoon was resuming and turned back to the cartoon again. The avatar's voice over was pre-recorded by a male team member who was not involved in this study and therefore unknown to the child. During this task, we mostly measured the time spent on the Penguin cartoon and the time spent on the avatar's face. We also measured the time to orient towards the face during pauses in both conditions.

**Figure 3** - Screenshot of Task 2 with the avatar on the right side of the screen and the Penguins cartoon playing on the left side.

**Task 3** (see Fig.4)**:** During this task we presented social stimuli in the form of real people doing various actions (e.g. smiling toward the screen, dancing, being surprised) on one side of the screen and a "distractor" on the other side of the screen. The videos of people realizing actions were all free of right videos. The simplest actions were selected and actions towards the screen to simulate interaction with the child were prioritized. As for the distractor, there were 4 different abstract shapes that were later modified regarding their colors to match the number of 26 trials. These distractors were here to keep children who might lose interest in a task that only shows social stimuli. We decided to include different versions to also avoid potential habituation and loss of interest even for this distractor.

The task included a total of 26 stimuli displayed for 10 seconds each. Again, a centering cross was displayed during one second between stimuli. Total duration of the task was about 5 minutes. Regarding the gaze-contingent aspect of this task, for the remediation group, social stimuli were reinforced positively when gazed at. Here they were "activated" by displaying them in a colorful version (see Fig.4 a) in addition to a playful childish song playing in the background. When not looked at, social stimuli were presented in a scrambled way, showing only the overall shape in white (see Fig.4 b) at first, and music stopped after 0.75s. In the control group, we previously randomly generated timepoints and associated duration (between 1-2 seconds) for each session. The stimuli were deactivated during these timepoints and reactivated automatically by the end of the associated duration. In this task, we measured the time spent on the social and non-social stimuli by splitting the screen into two AOIs. We also measured the time to gaze back or at a stimulus that deactivates in the remediation group.

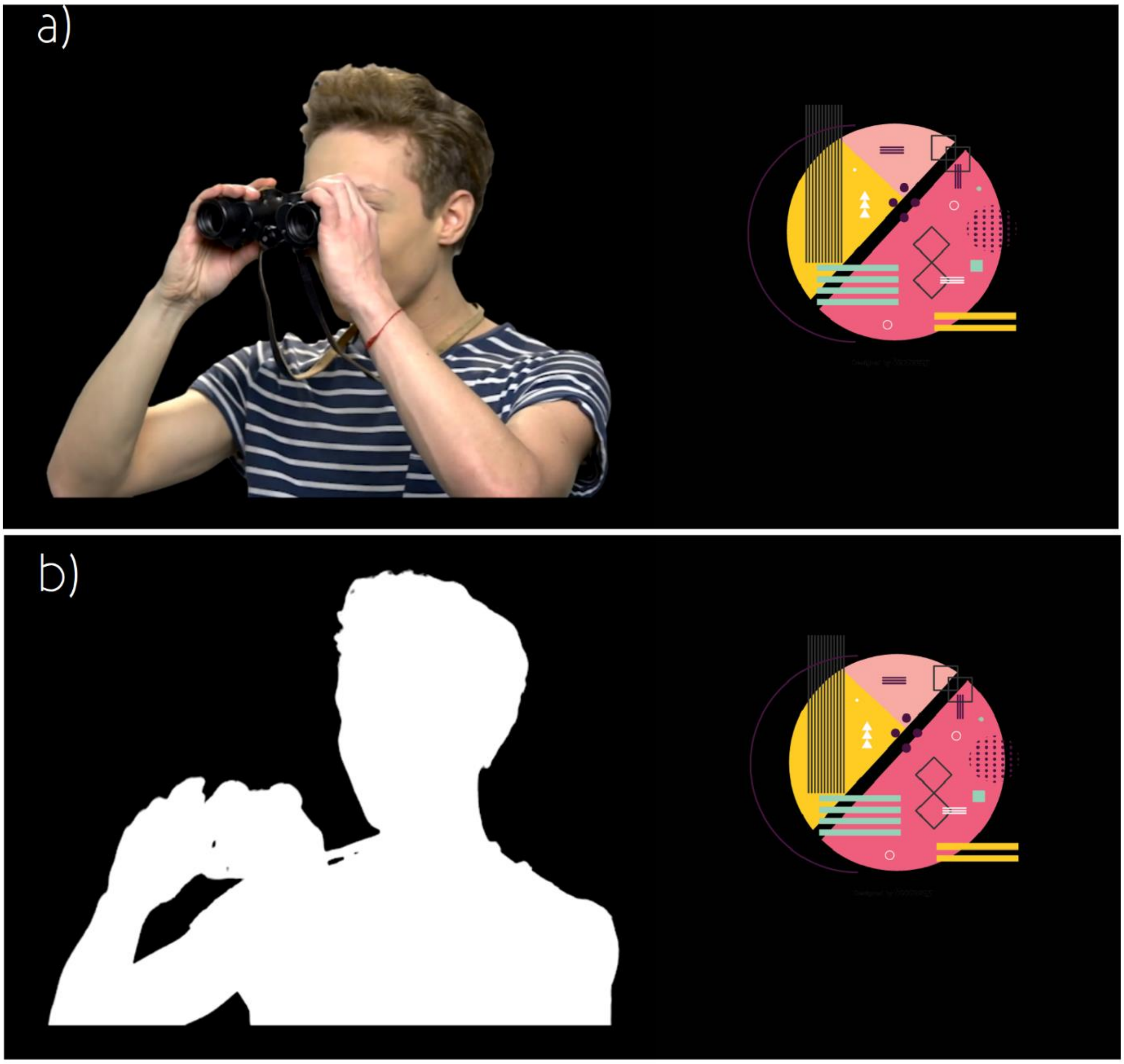



**Figure 4** - Screenshot of Task 3. **a)** Screenshot of an activated stimulus after being looked at displayed in full color mode with music playing **b)** Screenshot of a deactivated stimulus with no music in the background

**Task 4** (see Fig.5)**:** This task was inspired by Wang et al. (2020) who encouraged children with ASD to look at relevant areas of a scene based on what typically developing children looked at when watching the same movie. During this task, children watched a cartoon of Trotro lasting approximately 3min30sec. As this cartoon is also part of our longitudinal protocol (see Franchini et al. 2018), 38 typically developing preschoolers from 1.4 years to 5.5 years previously watched this cartoon. From their visual exploration, we extracted significant AOIs for each second of the cartoon. These AOIs were recoded as coordinate to correspond to trigger areas for the gaze-contingent part. Therefore, children who underwent the remediation watched Trotro in a clear fashion (see Fig.5 a) as long as they gazed at the previously extracted AOIs from TDs' exploration patterns. When deviating from the norms, in other words looking outside of the AOIs, for more than 1 second, a scrambled version of Trotro was displayed instead of the clear one (see Fig.5 b). This scrambled version consisted of an inverted shadow heatmap. This scrambled version only showed the areas observed by TD children while the rest of the scene was masked. A prolonged gaze within the normative AOIs restored the clear version of Trotro. By doing so we aimed to gradually reorient the attention of our children with ASD to the socially relevant part of a cartoon. For the control group, we previously randomly generated timepoints and durations for each session. As for the other task, when reaching the timepoint, Trotro was presented in the scrambled version for the total associated duration with no possibility to restore it by looking at the AOIs. During this task, we measured the time spent on the contingent AOIs, but we also looked at the time to gaze back to it when deactivated in the remediation group.

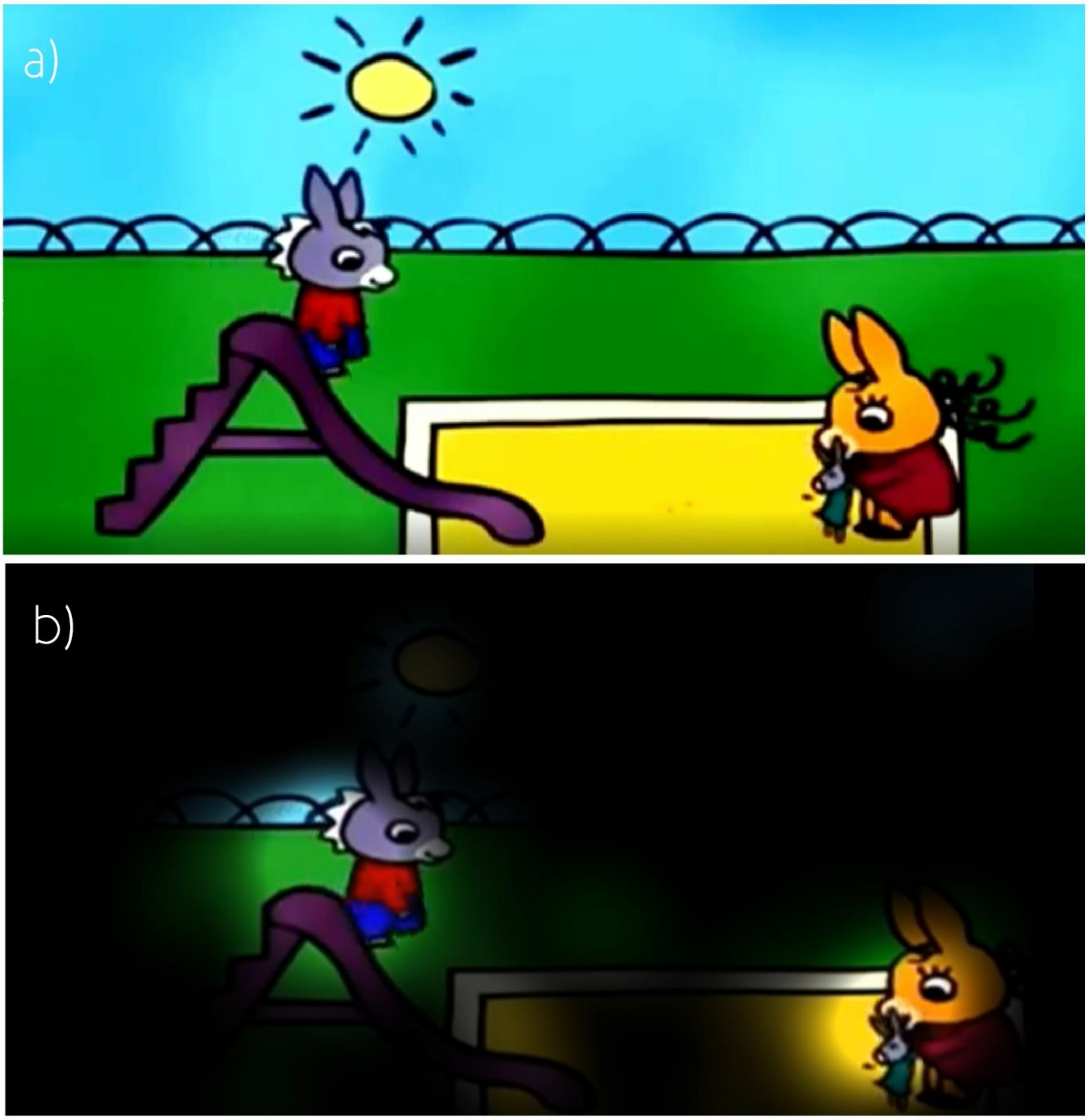



**Figure 5 -** Screenshot of Task 4 **a)** Screenshot of Trotro cartoon playing in a clear fashion **b)** Screenshot of the scrambled Trotro playing when gazing outside the normative AOIs.

*Outcome measures*

We used changes over the course of session within our 4 remediation tasks as outcomes measures. But we also wanted to measure if changes during and across the session could generalize. To investigate this, we used 3 different eye-tracking tasks as baseline/outcome measurements.

BiovsNonBio (see Fig.6): The first is a visual preference eye-tracking task, which has been used in our research lab (Franchini et al., 2016) and inspired by Pierce's studies (2011, 2016). This task has shown some stability in children's preference and is regularly analyzed as a potential predictor/moderator in children's response to intervention (Robain et al. 2020). Studies on this type of task have greatly influenced research in eye-tracking and autism. Results generally describe a lack of preference for social stimuli in children with ASD. In addition, it is generally reported that a subgroup of children with ASD, with more symptoms, show a strong preference for non-social information. Such a preference for non-social information in very young children is thus generally interpreted as a red flag of atypical development. We used the time spent on the social part of the screen as a measure of generalization of our intervention.

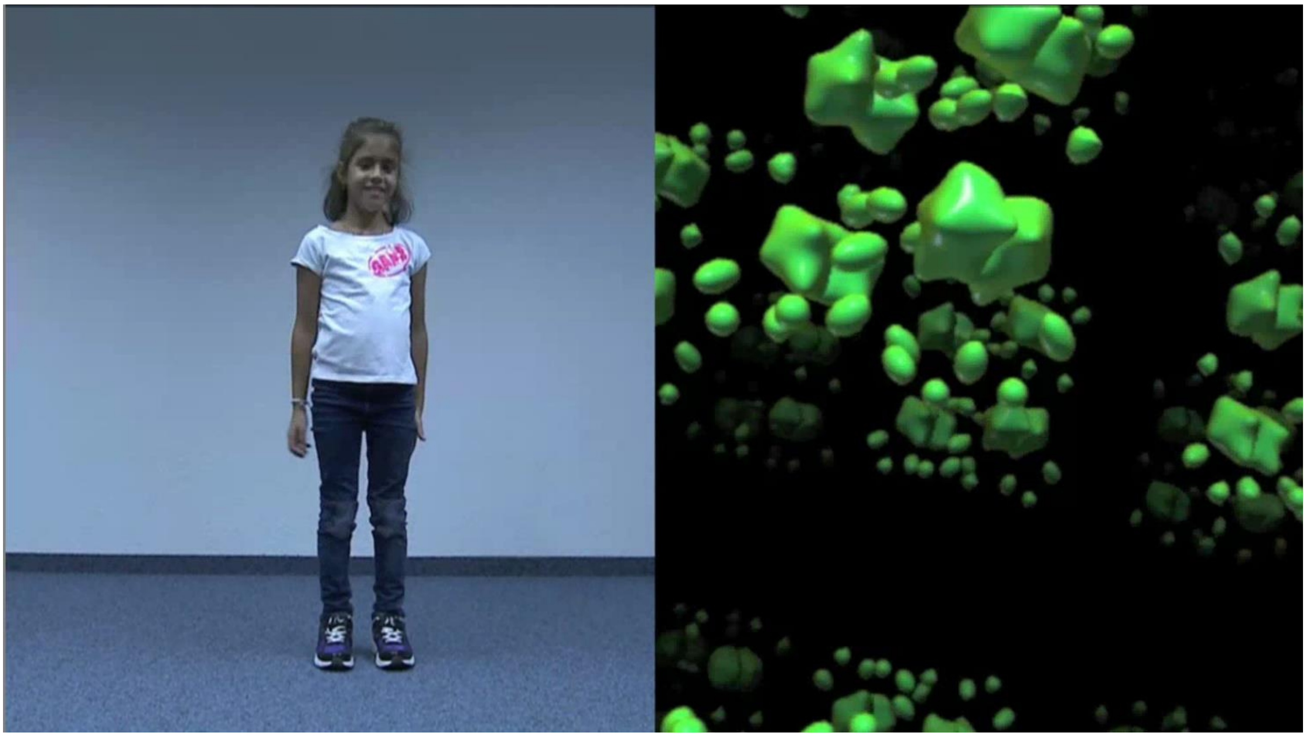


Figure 6 - Screenshot of the BiovsNonBio task with social stimulus on the left and non-social stimulus on the right side of the screen

Cartoons (see Fig.7): The second is a task similar to the first that presents social and non-social stimuli imagined for very young children. Here, the stimuli are cartoonish and simple, and were designed to have identical movements, a criticism regularly made to the previous task. The idea is therefore to be able to measure the social attention of very young children while using more controlled stimuli. Results from a sample of 110 children, 90 of whom have ASD, with an average age of 3 years demonstrated that children with ASD show equal interest in social and non-social stimuli when presented as cartoons (Robain et al. 2022). However, we identified numerous correlations between the way these stimuli are explored and developmental difficulties, suggesting that despite similar overall attention time, visual attention to these stimuli differs. We here again used the time spent on the social part of the screen as a measure of generalization of our intervention, despite expecting lesser changes to none compared to the first one.

Figure 7 - Screenshot of the Cartoon task with the social stimulus on the right and non-social stimulus on the left side of the screen

Direct speech (see Fig.8): The last task that we used was a task of attention to a woman that speaks directly to the child. The purpose of this task was to measure attention to a face during a direct interaction, potentially more engaging, even for children with ASD. A study, by our group, of 95 children with ASD and 16 typically developing children aged approximately 2.75 years showed that higher attention time to the face was associated with better skills in these same children (Latrèche et al., 2021). We therefore used the time looking at the face as our primary measure for this task.

**Figure 8 -** Screenshot of the Direct Speech task with a woman talking directly to the screen

In addition to these eye-tracking tasks, we also asked parents to fill questionnaires at the beginning and at the end of the intervention:

Social Responsiveness Scale - 2nd edition (SRS-II, Constantino et al., 2003): This standardized questionnaire is designed to measure the presence and severity of social difficulties in children with autism. We used the standardized scores in the different domains as a measure of progress over time.

Eye Contact Avoidance Scale (ECAS, Hall & Venema, 2017): Although originally developed for individuals with Fragile X syndrome, this questionnaire includes questions appropriate for individuals with ASD as it assesses eye-contact avoidance behaviors. We therefore used the subscores from this questionnaire as a measure of progress regarding eye-contact.

Finally, we developed a questionnaire for this study to track progress from one session to another according to parental point of view namely the Progress Questionnaire. The questions included several domains such as eye-contact, restricted repetitive behavior, social attention. Parents were asked to estimate the progress of the child compared to the beginning of the intervention.

*Behavioral measures*

As mentioned above, participants were recruited though CCSA, which implies that they were assessed using multiple standardized tests, to confirm diagnosis for example. We took advantage of these by investigating those behavioral measures and their potential relationship with the eye-tracking data collected during the study. We ended up getting symptom severity measure, developmental scores, and adaptive scores through the following tests:

Autism Diagnostic Observation Schedule - Second edition (ADOS-2, Lord et al., 2012): This assessment is widely used as part of ASD diagnosis. Therefore, all children with a diagnosis completed this assessment with a CCSA professional. The scores from the ADOS allowed us to get calibrated severity scores from (Gotham et al., 2009; Hus et al., 2014) which give Restricted and Repetitive Behaviors (RRB), Social Affect (SA) and Total severity scores.

Mullen Scales of Early Learning (MSEL, Mullen, 1995): The MSEL is a test that assesses children across developmental domains. This test compares scores to typically developing children. We used scores from all domains as developmental scores and included them as a covariate in our statistical models.

Vineland Adaptive Behavior Scale, 2nd edition (VABS-II, Sparrow et al., 2005): This test is a standardized questionnaire administered by an examiner to parents. The domains assessed include Communication, Autonomy in Daily Life, Socialization, and Motor Skills.

Autism Diagnostic Interview revised (ADI-R, Lord et al., 1994): This questionnaire focuses on the early symptoms of autism. Along with the ADOS-2, this questionnaire allows for confirmation of the presence of a diagnosis in a child.

*Hypothesis of the study*

We expect children in the remediation group to improve their attention regarding social stimuli in our non-contingent eye-tracking tasks. We also expect parents to report a decrease in problematic behavior on the SRS-2, decrease in eye-contact avoidance for the ECAS, progress over time on the follow-up questionnaires. We expect children to look more towards social stimuli over time during our gaze-contingent tasks. We also expect that children with lower developmental skills or/and higher levels of symptoms will benefit more from the intervention.  Regarding the control group, we do not expect any changes regarding their scores on any eye-tracking tasks or parental questionnaires. We would expect groups to be equivalent at the beginning of the intervention regarding their social orienting percentage on the various tasks but significantly different by the end of the intervention, in favor of the intervention group.

*Statistical analysis*

In order to explore all the data from our study, we used two-factors ANOVAS to investigate changes over time. We also conducted t-tests to explore differences between and within groups. Finally, we also used partial correlation to look at the association between changes over time and behavioral measurement at baseline. We excluded all bad quality data by applying a 50% threshold as a standard cut-off. For example, for every eye-tracking task, if a child did not pay attention to the screen for at least half of the task's duration, data were excluded. If within a valid task (watch time above 50%), trials were not watched for at least 50% of their own duration (usually 10s for tasks including trials), we excluded these trials and calculated the mean only using valid trials.

## Preliminary results

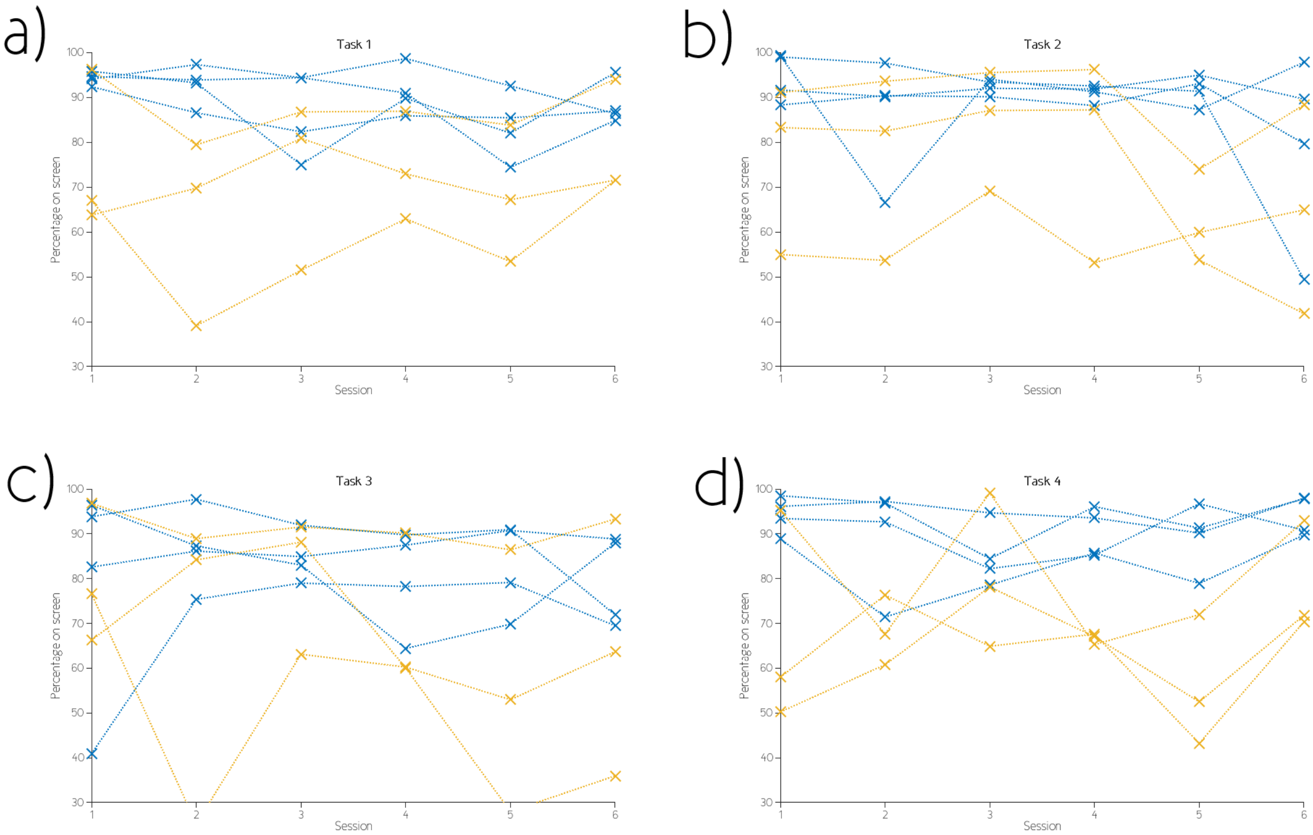



**Figure 9** - Percentage of time spent on screen per task. **a)** Percentage of time spent on screen during Task 1 **b)** Percentage of time spent on screen during Task 2 **c)** Percentage of time spent on screen during Task 3 **d)** Percentage of time spent on screen during Task 4. *Yellow lines represent participants from the SHAM group, blue lines represent participants from the REM group*

As a first step, we checked the percentage of time spent on the screen for each task within our groups. We would ideally have an equivalent percentage of time between groups even though we expect children in the SHAM group to exhibit less time on screen due to less interactivity with the task.

A two-factor ANOVA was conducted for each of the four tasks to investigate the effects of group and time, as well as their interaction, on the dependent variables. Across all tasks, a significant group effect was observed (see Fig.9): Task 1 ($F(1, 30) = 23.18$, $p < .001$), see Fig.9 a; Task 2 ($F(1, 30) = 11.40$, $p < .01$), see Fig.9 b; Task 3 ($F(1, 30) = 4.44$, $p < .05$), see Fig.9 c; and Task 4 ($F(1, 30) = 37.11$, $p < .001$, see Fig.9 d). However, no significant main effect of time or interaction effect between group and time was found in any of the tasks (all $p > .05$). Notably, only in Task 1 did paired t-tests reveal a tendential decrease in time spent on screen for the REM group from the first to the last session (mean baseline = 94.19, mean outcome = 88.40; $p = .06$), which was not observed in the control group. In all other tasks, unpaired and paired t-tests indicated no significant difference at baseline between the groups, as well as no differences within groups from the start to the outcome (all $p > .05$).

*Task 1*

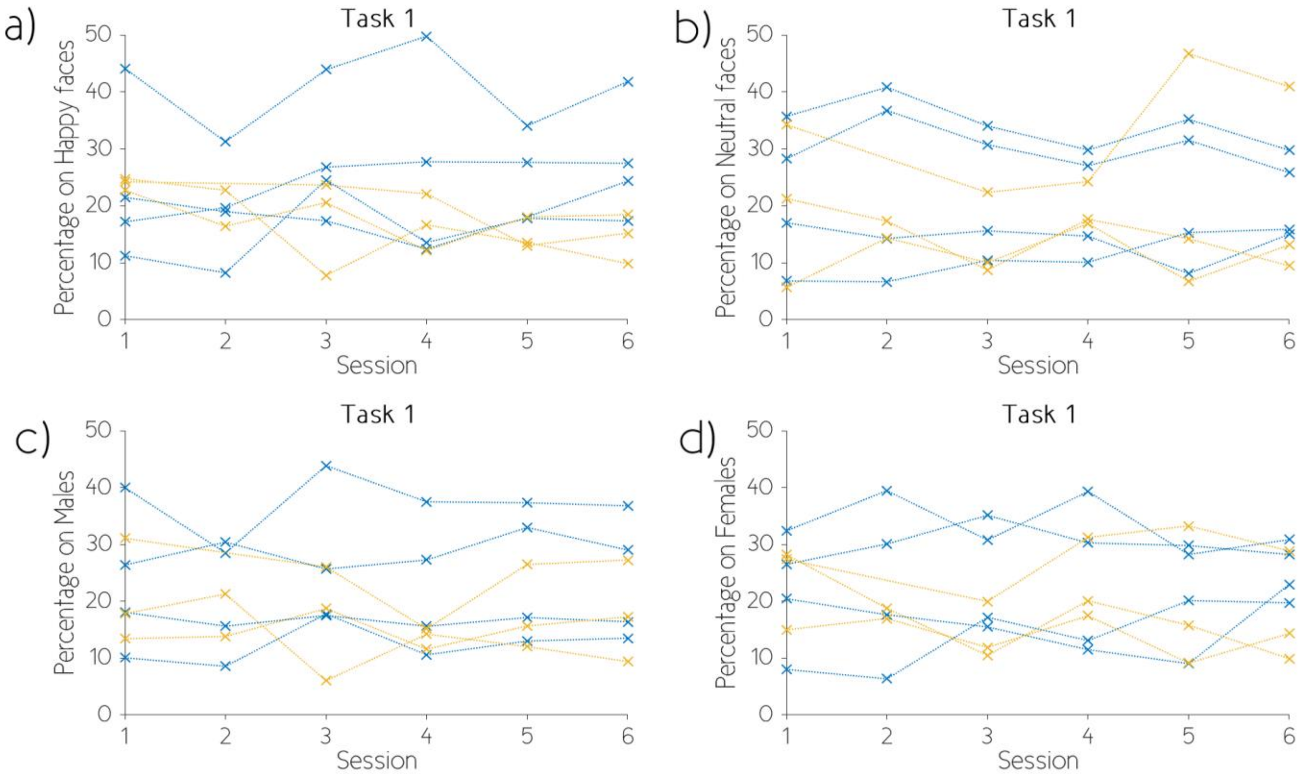
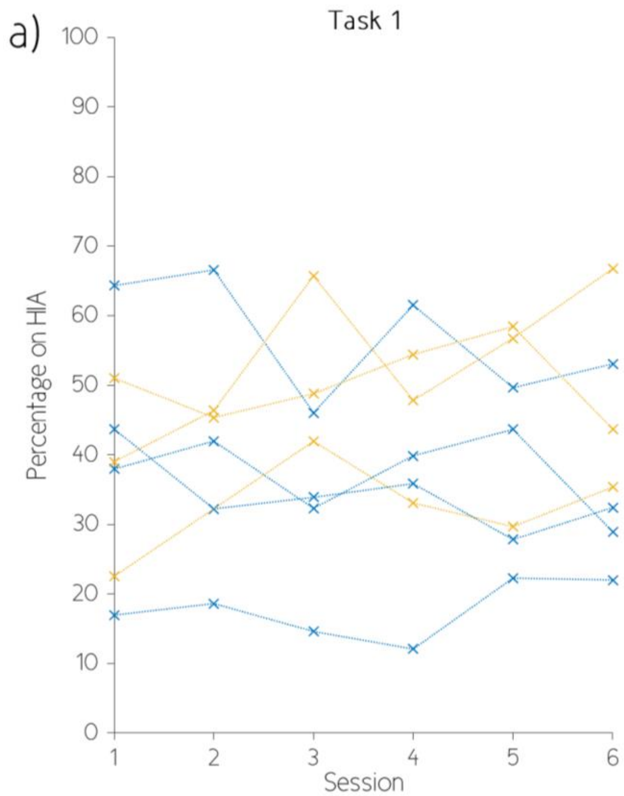



**Figure 10 -** Percentage of time spent on faces by categories by session. **a)** Percentage of time spent on Happy faces by session **b)** Percentage of time spent on Neutral faces by session **c)** Percentage of time spent on Male faces by session **d)** Percentage of time spent on Females by session

A series of two-factor ANOVAs were conducted to investigate the effects of group and time, as well as their interaction, on various dependent variables. For happy faces, a significant group effect was found ($F(1, 29) = 4.74$, $p < .05$, see Fig.10 a), indicating differences between groups in favor of the REM group, while no significant time effect or interaction effect was observed. In contrast, for neutral faces, females and males, no significant effects were found for group, time, or interaction, and no differences were observed in t-tests (all $p > .05$).



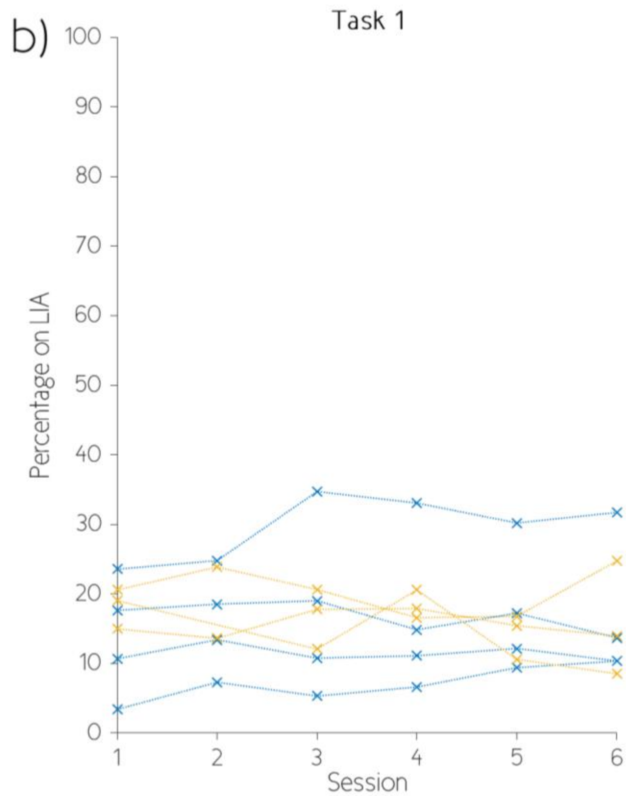




**Figure 11 -** Percentage of time spent on objects by categories by session. **a)** Percentage of time spent on HIA objects by session **b)** Percentage of time spent on LIA objects by session

Regarding object categories, for HIA, the group effect showed a trend towards significance ($F(1, 29) = 3.72$, $p = .0635$, see Fig.11 a), suggesting potential differences between groups, but no significant time effect or interaction effect was found. This trend was driven by a global decrease of time spent on HIA in the REM group and an increase in the SHAM group. No effects were significant within the LIA objects.

Overall, the ANOVAs revealed significant group effects only for happy faces in favor of the REM group and a trend for increased time spent on HIA in the SHAM group, with no other significant effects or differences observed.

*Task 2*

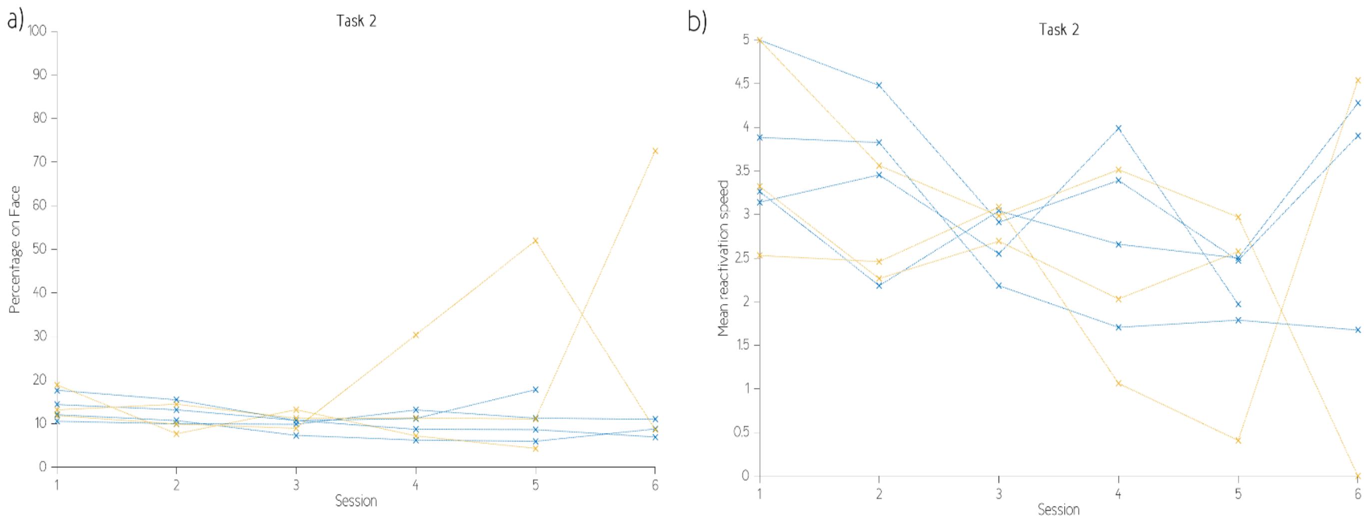



**Figure 12 –** Results of Task 2 **a)** Percentage of time spent on the avatar's face by session **b)** Mean orientation time towards the avatar during pauses by session

A two-factor ANOVA was conducted to investigate the effects of group and time, as well as their interaction, on the dependent variables: time spent on avatar's face, time spent on the penguins and time to reactivate the cartoon when paused. We identified significant effect of group for time spent on the face ($F(1, 28) = 4.87$, $p < .05$; see Fig.12 a) and for time spent on the penguins ($F(1, 28) = 5.49$, $p < .05$), indicating that there were differences between the groups. The REM group showed higher time spent on the penguins and lower time on the face compared to the SHAM group. However, the main effect of time was not statistically significant, suggesting that the dependent variable did not change significantly over time. Additionally, there was no significant interaction effect between group and time, indicating that the pattern of change over time did not differ between the groups (all $p > .05$). We did not identify any effect of time, group nor interaction regarding the time to reactivate the cartoon despite a trend toward a general decrease over time (see Fig .12 b). Finally, t-tests did not identify any differences at baseline between groups or differences from baseline to outcome measures within groups.

*Task 3*

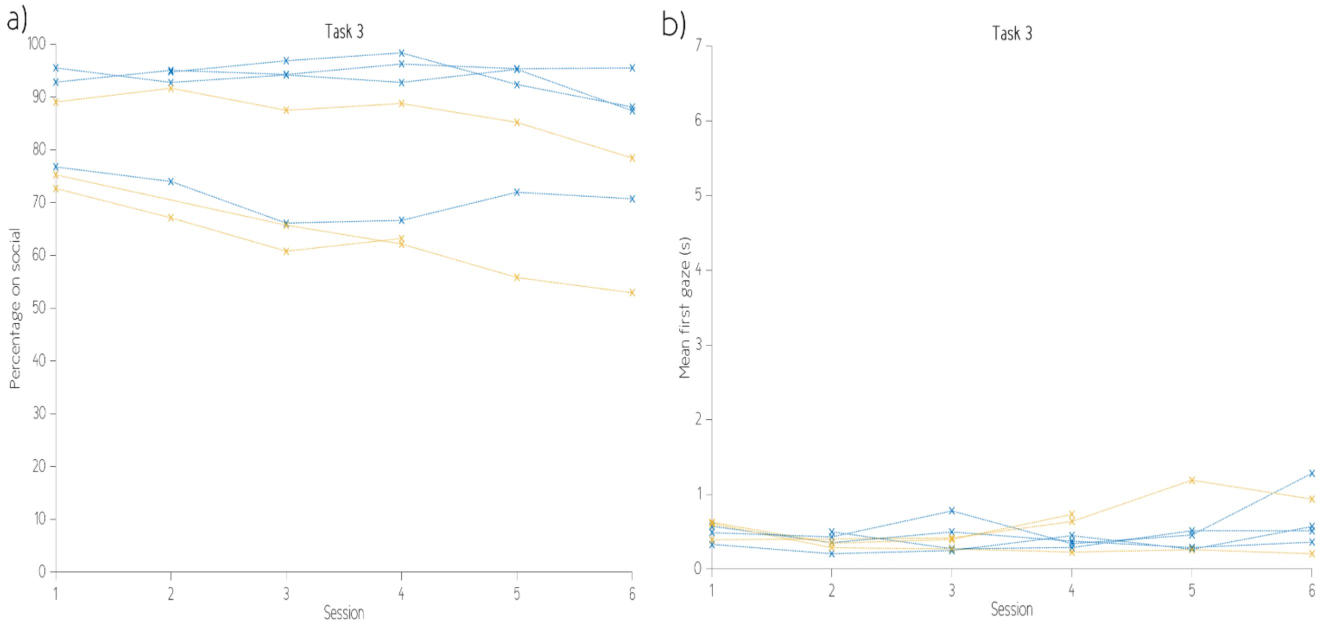



**Figure 13 -** Results of Task 3 **a)** Percentage of time spent on the social side of the screen by session **b)** Mean first gaze towards social side of the screen by session.

A two-factor ANOVA was conducted to investigate the effects of group and time, as well as their interaction, on the time spent on the social side of the screen. The group effect was found to be statistically significant ($F(1, 26) = 11.44$, $p < .01$; see Fig.13 a) indicating that there were differences between the groups in favor of the REM group spending more time looking at the social side compared to the SHAM group. However, the main effect of time was not statistically significant, $F(5, 26) = 0.32$, $p > .05$, suggesting that the dependent variable did not change significantly over time. Additionally, there was no significant interaction effect between group and time, $F(5, 26) = 0.16$, $p > .05$, indicating that the pattern of change over time did not differ between the groups. We did not observe any effect of time, group nor interaction when performing ANOVA to investigate the effect on the speed to look at the social side of the screen (all $p > .05$, see Fig.13 b). T-tests did not highlight any differences at baseline between groups nor any within group differences from start to outcome, despite a general trend towards decrease of time spent on social within the SHAM group.

*Task 4*

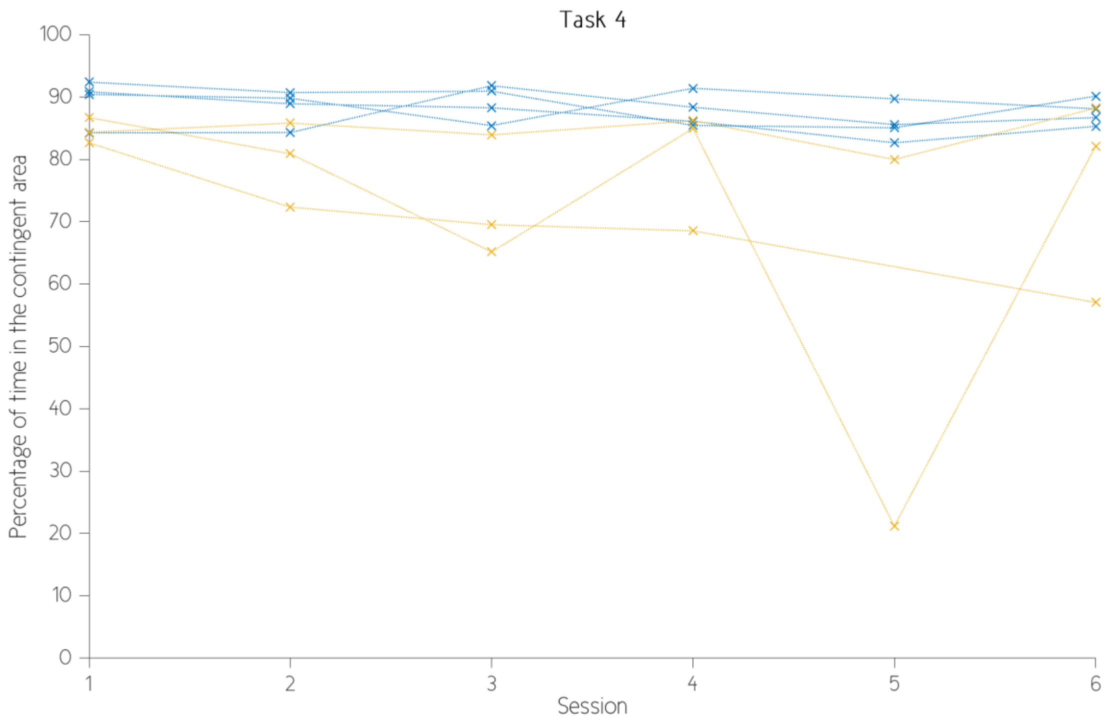



**Figure 14 -** Percentage of time spent on the contingent AOI by session.

A two-factor ANOVA was conducted to investigate the effects of group and time, as well as their interaction, on the time spent on the TD AOIs. The group effect was found to be statistically significant ($F(1, 29) = 19.50$, $p < .001$, see Fig.14) indicating that there were differences between the groups, in favor of the REM group spending more time within the TD AOIs, compared to the SHAM group. The main effect of time showed a trend towards significance, $F(5, 29) = 2.47$, $p = .0552$, suggesting a global decrease within the TD AOIs over time. However, there was no significant interaction effect between group and time, $F(5, 29) = 1.72$, $p > .05$, indicating that the pattern of change over time did not differ between the groups.

### *Baseline/Outcome eye-tracking tasks*

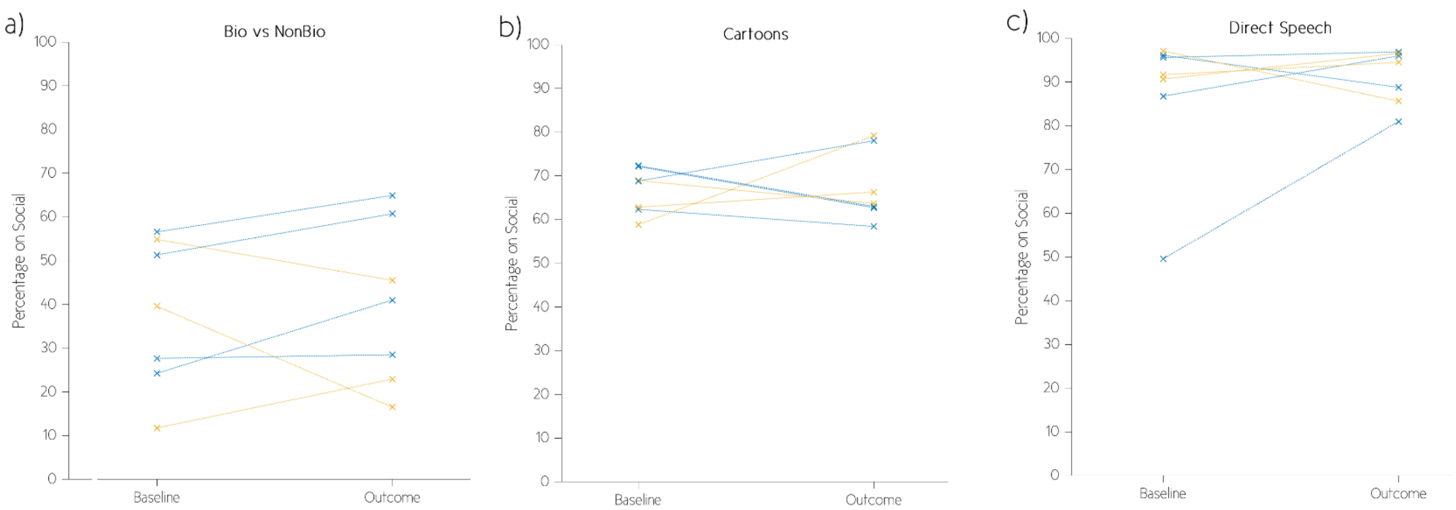


**Figure 15 -** Results from the non-contingent eye-tracking tasks **a)** Percentage of time spent on the social side of the screen during the BiovsNonBio task **b)** Percentage of time spent on social during the Cartoons task **c)** Percentage of time spent looking at the face during the Direct Speech task.

A two-factor ANOVA was conducted to investigate the effects of group and time, as well as their interaction, on the time spent on the Percentage of time spent on the social side of the screen during the BiovsNonBio task, Percentage of time spent on the social side of the screen during the Cartoon task and the percentage of time spent on the Direct speech task. We did not identify any significant effect of group, time nor interaction on any of the 3 tasks (see Fig.15). No differences were significant regarding t-test as well, suggesting no difference between groups at start or within groups between baseline and outcome (all p > .05).

*Questionnaires*

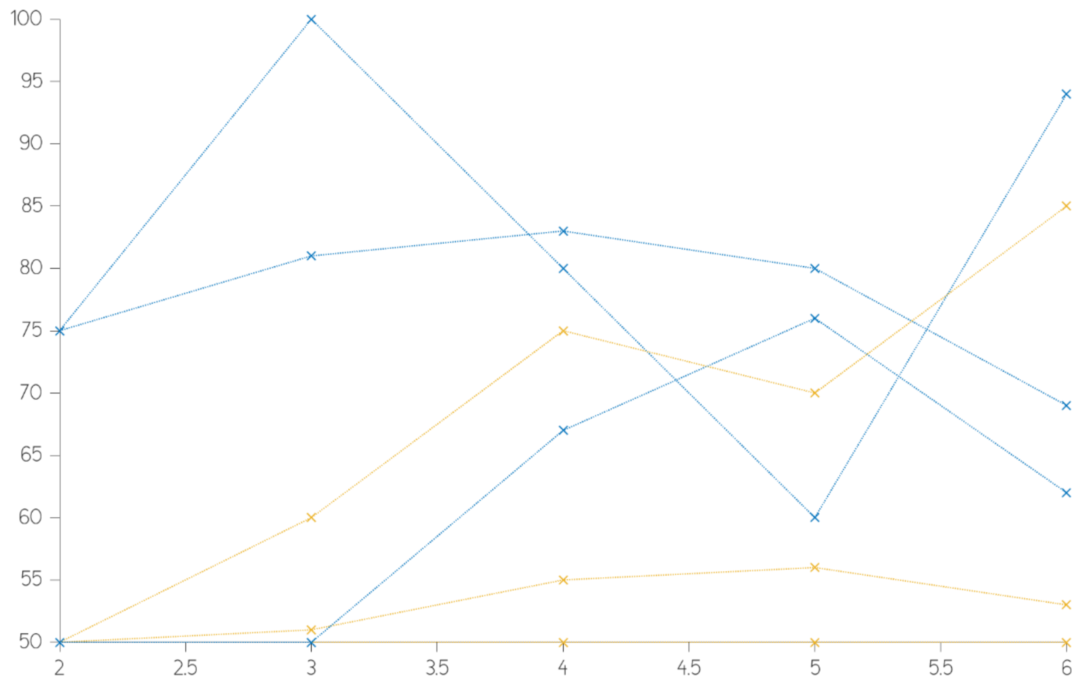



**Figure 16 -** Progress reported by parents regarding the number of smiles from their children since the beginning of the intervention, by session.

We performed two-factor ANOVA to investigate the effects of group and time, as well as their interactions on all the scores of our questionnaires: the SRS-II, the ECAS and our evolution questionnaire specially designed for this study. As of now, we did not identify any significant effect of time, group nor interaction on any of our questionnaire variables (all p > .05). Yet, there was a trend for a group effect regarding the amount of smiles within the progress questionnaire ($F(1,34) = 3.934$, p = .058, see Fig.16) in favor of the REM group compared to the SHAM group. In other words, parents tend to report increased smiles frequency within the children following the REM.

## Discussion

Due to the very preliminary nature of these results, the discussion has not yet been written for this paper. A general discussion of the preliminary results and first impressions can be found in the thesis manuscript in section 3.3.

## 6.7 Video examples of eye-tracking tasks

Please scan this QR code to access video examples of all eye-tracking tasks discussed during this work.