Investigating executive functions, memory and the effect of stimulant medication on cognitive performance in 22q11.2 deletion syndrome

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INVESTIGATING EXECUTIVE FUNCTIONS, MEMORY AND THE EFFECT OF STIMULANT MEDICATION ON COGNITIVE PERFORMANCE IN 22Q11.2 DELETION SYNDROME

Étude des fonctions exécutives, de la mémoire et de l'effet d'un traitement de stimulant sur les processus cognitifs dans le syndrome de la microdélétion 22q11.2

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INVESTIGATING EXECUTIVE FUNCTIONS, MEMORY AND THE EFFECT OF STIMULANT MEDICATION ON COGNITIVE PERFORMANCE IN 22Q11.2 DELETION SYNDROME

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Abstract

Chromosome 22q11.2 deletion syndrome (22q11DS) is a genetic condition associated with an increased risk for developing psychiatric disorders (including schizophrenia) and a specific cognitive profile. Because of its relatively homogeneous genetic origin, this population is considered a model for the study of the emergence of psychosis and schizophrenia spectrum disorder. In the first part of this work, we aim to specify the neuropsychological profile of this population with a particular interest for executive functions and memory. In the second part, we examine the benefits of stimulant medication on cognitive processes.

In recent years, numerous studies have been carried out to identify and describe the neuropsychological profile of this population and to identify the strengths and weaknesses of these individuals. In general, executive functions and attention are identified as weaknesses in the 22q11DS profile. However, due to the wide variety of tasks used in the different studies, the current literature does not allow to conclude whether some sub-domains are more affected than others. In addition, age-related changes have been examined in only a few studies, giving only a partial view of the overall developmental profile so far. Studies 1 and 2 aim to delineate the developmental trajectories of several sub-domains of executive functions and attention in a longitudinal sample of children, adolescents and young adults with 22q11DS.

On the topic of memory, visual memory is identified as a weakness, while verbal memory appears to be relatively preserved. However, the observations coming from individuals with 22q11DS and their caregivers point towards forgetfulness and long-term memory loss. Thus, in Study 3 we challenge the general hypothesis of preserved long-term verbal memory. We develop a measurement tool to explore long-term memory processes, in particular memory retention and forgetting after a prolonged period of time (up to one month). In Study 4 we examine the retention of verbal and non-verbal information in memory after a delay of one month, with and without potential interference of reconsolidation processes in memory.

Finally, as previously mentioned, 22q11DS is associated with an increased risk of psychiatric disorders. This implies that taking medication is frequent in this population. However, very few studies have been interested in measuring the medium- and long-term effects of these treatments on cognitive processes in this population. Thus, in study 5 we evaluate the benefits of a stimulant treatment (methylphenidate) on executive functions, attention and memory in the context of 22q11DS.

Résumé en français

La microdélétion 22q11.2 (del22q11) est un syndrome génétique associé à un risque augmenté de troubles psychiatriques (notamment la schizophrénie) et un profil cognitif particulier. De par l'origine génétique relativement homogène, cette population est considérée comme un modèle d'étude de l'émergence de la psychose et de la schizophrénie. Dans ce travail nous nous intéresserons d'une part à préciser le profil neuropsychologique de cette population avec un intérêt particulier pour les fonctions exécutives et la mémoire. D'autre part nous examinerons les bénéfices d'une médication de stimulant sur les processus cognitifs.

Ces dernières années, de nombreuses études se sont appliquées à identifier et décrire le profil neuropsychologique de cette population et d'identifier les forces et faiblesses de ces individus. De manière générale, les fonctions exécutives et l'attention sont identifiées comme des faiblesses dans le profil de la del22q11. Cependant, en raison de la grande variété des tâches utilisées dans les différentes études, la littérature actuelle ne permet pas de conclure si certains sous-domaines sont plus affectés que d'autres. En outre, les changements liés à l'âge n'ont été examinés que dans quelques rares études, ne donnant jusqu'à présent qu'une vue partielle du profil de développement global. Les études 1 et 2 visent à délimiter les trajectoires de développement de plusieurs sous-domaines des fonctions exécutives et de l'attention dans un échantillon longitudinal d'enfants, d'adolescents et de jeunes adultes avec une del22q11.

Dans le domaine de la mémoire, la mémoire visuelle est identifiée comme une faiblesse, alors que la mémoire verbale semble relativement préservée. Toutefois, les observations des individus porteurs de la de22q11 et de leur entourage rapportent des oublis fréquents et la perte de l'information à long terme. Ainsi dans l'étude 3 nous remettons en cause l'hypothèse générale d'une mémoire verbale à long terme épargnée. Grace au développement d'un outil de mesure permettant d'explorer les processus de mémoire à long terme, en particulier la rétention de la mémoire et d'oubli après un délai prolongé (jusqu'à un délai d'un mois). Dans l'étude 4

nous examinerons la rétention de l'information verbale et non verbale en mémoire après un délai d'un mois, avec et sans interférence potentielle des processus de reconsolidation en mémoire.

Finalement comme évoqué précédemment, la del22q11 est associée à un risque augmenté de troubles psychiatriques. Ceci implique que les traitements médicamenteux sont fréquents dans cette population. Cependant, très peu d'études se sont intéressées à mesurer les effets à moyen et long-terme de ces traitements sur les processus cognitifs dans cette population. Ainsi dans l'étude 5 nous proposons d'évaluer les bénéfices d'un traitement de stimulant (le méthylphénidate) sur les fonctions exécutives, l'attention et la mémoire dans le contexte de la del22q11.

List of abbreviations

22q11DS	22q11.2 deletion syndrome
ABC	Adaptive Behavior Composite score
ADHD	Attention Deficit and/or Hyperactivity Disorder
ALF	Accelerated Long-term Forgetting
B-H	Benjamini-Hochberg correction
BPRS	Brief Psychiatric Rating Scale
BRI	Behavioral Regulation Index
CANTAB	Cambridge Neuropsychological Test Automated Battery
CCER	Comité Cantonal d'Éthique de la Recherche (Swiss Ethical Committee of Geneva)
CNV	Copy-Number Variation
COMT	Catechol-o-methyltransferase
CPT	Conners' Continuous Performance Test
CTT	Color Trails Test
CVLT-C	California Verbal Learning Test for children
DICA-R	Diagnostic Interview for Children and Adolescents-Revised
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography
EDS	Extra-Dimensional Shift
EF	Executive Functions
FSIQ	Full-Scale Intellectual Quotient
fMRI	functional Magnetic Resonance Imaging
GC-ML-DG	Granulate Cells of the Molecular Layer of the Dentate Gyrus
GEC	Global Executive Composite

HATA	Hippocampus-Amygdala Transition Area
HRT	Hit Reaction Time
IED	Intra-/Extra-Dimensional Shift task
IQ	Intellectual Quotient
K-SADS-PL	Schedule for Affective Disorders and Schizophrenia for School-age children Present and Lifetime
Mb	Mega base
MI	Metacognitive Index
MPH	Methylphenidate
NICE	National Institute for Health and Care Excellence
Omega-3	Long-chain omega-3 polyunsaturated fatty acids
PANSS	Positive and Negative Syndrome Scale
PFC	Prefrontal Cortex
PPVT	Peabody Picture Vocabulary Test
QF-PCR	Quantitative Fluorescent Polymerase Chain Reaction
QTc	Corrected QT
RAVLT	Rey Auditory Verbal Learning Test
SCID-I	Structured Clinical Interview for DSM-IV Axis I
SD	Standard Deviation
SIPS	Structured Interview for Prodromal Syndromes
SSRI	Selective Serotonin Reuptake Inhibitor
SSRT	Stop Signal Reaction Time
SST	Stop Signal Test
SWM	Spatial Working Memory test
UHR	Ultra High Risk

VABS	Vineland Adaptive Behavior Scales
VCFS	Velo-Cardio Facial Syndrome
WAIS	Wechsler Adult Intelligence Scale
WISC	Wechsler Intelligence Scale for Children
WRAML	Wide Range Assessment of Memory Learning

Table of content

I. INTRODUCTION

Chromosome 22q11.2 deletion syndrome (22q11DS) is a genetic condition associated with structural and functional brain anomalies and an increased risk for developing psychiatric disorders (Padula et al., 2015; Rogdaki et al., 2020; Schneider, Debbané, et al., 2014). Studying the complex cognitive profile that characterizes patients with 22q11DS and its atypical development with age provides insight into the association between cognition and psychopathology. The main objectives of this thesis are twofold, in the first part we aim to specify the neuropsychological profile of this population with a focus on executive functions and memory (long-term). In the second part, the aim is to move past the description of deficit and toward intervention by examining the benefits of stimulant medication on cognitive processes and clinical symptoms of inattention and hyperactivity.

1. General overview of 22q11DS

Historically, 22q11DS has been described in the literature since 1955 under different names such as Shprintzen Syndrome, Di George Syndrome or Velo-Cardio Facial Syndrome (VCFS) (Robin & Shprintzen, 2005). In 1992, a common genetic cause was identified enabling a common label for this genetic condition, despite the large variability of the phenotype (Robin & Shprintzen, 2005; Shprintzen, 2008). In the majority of cases (90%), the syndrome results from a hemizygous deletion of a 3 million base pairs (mega base, Mb) on the long arm of chromosome 22, at locus 11.2 (Guo et al., 2018; McDonald-McGinn et al., 2015). Smaller deletion of 1.5 or 2 Mb are also observed, but much less frequent and no link has been demonstrated between the size of the deletion and severity of the phenotype (McDonald-McGinn et al., 2015; Squarcione, Torti, Di Fabio, & Biondi, 2013). As most of the genes hemizygously deleted are expressed in the brain, it has been suggested that the deletion may disrupt processes required for proper brain development or function, leading to cognitive

impairment and increased risk for psychopathology (Karayiorgou, Simon, & Gogos, 2010; Maynard et al., 2003). Although it is a rare genetic condition, 22q11DS is the most common Copy-Number Variation (CNV) in humans and affects 1 in 3000-6000 births (Botto et al., 2003; Olsen et al., 2018; Oskarsdóttir, Vujic, & Fasth, 2004). However, it is estimated to occur in almost 1 in 1000 pregnancies (Grati et al., 2015). Transmission is *autosomal dominant*, meaning that the deletion can be passed on by either the father or the mother since the missing genes are not located on the sex chromosome and the presence of a single affected allele is sufficient for the syndrome to be expressed. At the present time, in most of diagnosed cases (72-91%), the deletion appears *de novo*, indicating that it is not inherited from one of the parents (Besseau-Ayasse et al., 2014; Cancrini et al., 2014; Ryan et al., 1997). Although with improved survival rates and higher reproductive fitness of 22q11DS carriers, inherited forms are expected to increase (McDonald-McGinn et al., 2015; McDonald-McGinn & Sullivan, 2011).

The phenotype of 22q11DS can express itself in very different ways (over 180 associated features described) and concerns vary during development (Philip & Bassett, 2011; Robin & Shprintzen, 2005; Swillen & McDonald-McGinn, 2015). Common signs leading to diagnosis in infancy and childhood include a combination, to varying degrees, of heart defects, chronic infections, hypocalcemia, nasal regurgitation, hyper-nasal speech, feeding difficulties, delays in language development and onset, and learning disabilities (McDonald-McGinn et al., 2015). A collaborative study including 228 patients with 22q11DS found that for 71% of patients diagnosis was made before the age of 2, with cardiac defects and hypocalcemia being the most relevant clinical features (Cancrini et al., 2014). For individuals diagnosed after 2 years old clinical manifestations raising suspicion were speech and language impairment, development delay, and recurrent infections, associated with characteristic facial features (small mouth, tubular nose, and minor ear anomalies).

During adolescence, cognitive and learning difficulties as well as the increased risk for psychopathology are at the forefront (McDonald-McGinn et al., 2015). In particular, the risk of developing schizophrenia spectrum disorder is estimated at 10% in adolescents (13-17 years), 25% in young adults (18-25 years) and more than 40% by the age of 26, making 22q11DS a unique model for the study of the emergence of psychosis (Rees et al., 2014; Schneider, Debbané, et al., 2014). The syndrome is also associated with a high prevalence for other disabling psychiatric disorders such as anxiety disorders, which affect 30-76% of individuals, and Attention Deficit and/or Hyperactivity Disorder (ADHD), which is observed in 37-45% of individuals (Antshel et al., 2006; Gothelf et al., 2013; Schneider, Debbané, et al., 2014; Young, Shashi, Schoch, Kwapil, & Hooper, 2011).

With regards to school and education, needs for educational assistance and specialized education are frequent and tend to increase with age (Mosheva et al., 2018). As children get older, the material and concepts to master become more abstract and some students are unable to keep pace without increasing dependence on special education staff and parents (Cutler-Landsman, 2020). To improve management and care for these students, a comprehensive picture of their neuropsychological profile is necessary. By studying cognitive performances, specific recommendation and rehabilitation tools can be tailored to fit individuals' needs. While cognitive abilities predicts school placement in children and adolescents, for adults, other predictors are at play (Mosheva et al., 2018). The authors showed that adaptive functioning (i.e., handling of everyday life demands) predicts employment more than cognitive abilities.

In sum, the 22q11DS phenotype is very broad and includes somatic, psychiatric and cognitive features. Moreover, this phenotype evolves with age bringing new challenges over time. Studying the cognitive profile of this syndrome in relationship to brain alterations in a developmental approach is a necessary step toward understanding the emergence of psychiatric disorders.

2. Advantage of a genetic model

The genetic origin of 22q11DS provides research with a number of advantages. First of all, it allows to identify a group of individuals with a relatively homogenous etiology leading to an increased risk for psychopathology. Indeed, diagnosis can potentially be done very early on, often before the onset of certain psychiatric illness. Additionally, once the diagnosis is made, longitudinal studies can follow patients to better understand the emergence and course of development of psychiatric disorders.

Secondly, a genetic model also provides with the opportunity to study factors that influence outcome. More specifically, by studying the neurocognitive and psychiatric phenotype of this population potential markers can be recognized and further used as intervention targets. For example, work from the international consortium including 829 patients with 22q11DS demonstrated that early cognitive decline of verbal intellectual abilities (verbal IQ) was suggested as a robust indicator for developing a psychotic illness (Vorstman et al., 2015). In a study examining the role of stress and coping mechanisms on psychosis, Armando et al. (2018) showed that dysfunctional coping strategies mediates the relationship between stress load and psychotic symptoms in 22q11DS individuals.

Finally, knowledge of the genes deleted from this locus can be used to generate etiologically valid animal models to better understand altered gene dosage. Animal models allow direct assessment of the impact of genetic factors on neural activity across multiple brain areas, where the currant human approach is limited (Karayiorgou et al., 2010). For example, in a mouse-model of 22q11DS called Df(16)A1$^{+/-}$ mice, disrupted long-range synchrony between the hippocampus and medial pre-frontal cortex have been demonstrated and related to impairment in a working memory task (Sigurdsson, Stark, Karayiorgou, Gogos, & Gordon, 2010). Furthermore, in another mouse-model of 22q11DS called LgDel$^{+/-}$ mice, hypo-excitability of a

subpopulation of inhibitory neurons (parvalbumin neurons) was identified as playing a role in altered neuronal synchrony in the hippocampus and possibly other brain regions (Marissal et al., 2018). Moreover, rescue of neuronal recruitment dysfunction together with cognitive deficits was demonstrated in LgDel$^{+/-}$ mice with a pharmacological treatment (D2 receptor antagonist) in a specific time window during late adolescence (Mukherjee, Carvalho, Eliez, & Caroni, 2019). A translational study evaluating the impact of long-chain omega-3 polyunsaturated fatty acids (omega-3) treatment found certain common results between LgDel$^{+/-}$ mice and 22q11DS patients (Armando et al., 2020). In addition to improve cognitive measures of distractibility in mice and humans, 22q11DS patients exposed to omega-3 treatment showed less risk of developing an Ultra High Risk (UHR) status and lower conversion rate to psychosis.

Altogether, a homogenous genetic origin provides a unique possibility to study the role of certain genes in the development of psychiatric disorders. Furthermore, translational research gives the opportunity to answer questions about the pathogenesis behind psychopathology and construct knowledge on potential pharmacological interventions.

3. Atypical brain development in 22q11DS

On the cerebral level, many studies have focused on the alterations observed in 22q11DS. Indeed, compared to healthy controls, morphological (enlarged ventricles), structural (grey and white matter anomalies) and functional (abnormalities of brain activity) differences are described (Rogdaki et al., 2020; Scarpazza et al., 2019; Sun et al., 2018).

At the structural level, white matter alterations in the form of a loss of volume (11-16%) as well as micro-structural defects are found (Da Silva Alves et al., 2011; Eliez, Schmitt, White, & Allan, 2000; Rogdaki et al., 2020; Simon et al., 2005; Sundram et al., 2010). These alterations are relatively extensive and involve most white matter fibers, with more marked alterations in

the median and frontal regions (Padula, Schaer, Scariati, Mutlu, et al., 2017; Scariati, Padula, Schaer, & Eliez, 2016). In addition, studies using tractography have shown abnormalities in the development of white matter fibers during childhood and adolescence (Jalbrzikowski et al., 2014; Padula et al., 2015). Secondly, structural alterations are also observed in grey matter, which also shows a reduction in volume (7.5%) (Eliez et al., 2000; Rogdaki et al., 2020). A recent study revealed that the grey matter thickness is generally increased in 22q11DS, except for the temporal and median regions, which show reductions (Sun et al., 2018). Furthermore, from a developmental perspective, two independent studies have shown a significant increase in cortical thickness in children with 22q11DS (compared to healthy controls), particularly in the prefrontal regions (Ramanathan et al., 2017; Schaer et al., 2009). However, from late adolescence onwards this relative increase is no longer visible, suggesting an excessive thinning of the prefrontal regions during adolescence, pointing towards altered brain maturational process in this population. Another consistent neuroanatomical feature of 22q11DS is the diminished volume of the hippocampi (Debbané, Schaer, Farhoumand, Glaser, & Eliez, 2006; DeBoer, Wu, Lee, & Simon, 2007; Kates et al., 2006; Scott et al., 2016). Recently, one study showed that 22q11DS patients with higher rates of psychotic symptoms undergo additional decrease in hippocampal volume during adolescence, a vulnerable period for the emergence of psychosis (Mancini et al., 2019).

At the functional level, many studies have looked at differences in activity when the brain is at rest (resting state) using either functional Magnetic Resonance Imaging (fMRI) or Electroencephalography (EEG). Both fMRI and EEG represent two complementary approaches to the investigation of brain function in terms of spatial and temporal resolution. By studying brain activity at rest, one of the questions of interest is how different regions of the brain are activated over time. When several regions are active simultaneously, it is hypothesized that this creates "networks" that allow communication between these different regions. The term

functional connectivity is commonly used to refer to the connection between these different active regions over time. In 22q11DS, fMRI results point to an alteration of both intra-network and inter-network connections (Padula, Schaer, Scariati, Maeder, et al., 2017). For example, a recent review of fMRI results revealed a predominant alteration in functional connectivity between the frontal, parietal and medial regions (Scariati et al., 2016). At the same time, EEG studies have shown an imbalance between different functional networks, characterized by an increase in the network responsible for the attribution of salience, at the expense of the fronto-parietal attentional network which is under-represented (Tomescu et al., 2014). Additionally, results from a longitudinal study suggest different developmental trajectories of early auditory sensory processing in 22q11DS and functional changes that emerge during adolescence, a critical period of increased risk for schizophrenia spectrum disorders (Cantonas et al., 2019).

More recently, several studies have examined the relationship between the presence of structural or functional brain alterations and psychotic symptoms or cognitive impairment observed in this population (Mancini, Zöller, Schneider, Schaer, & Eliez, 2020; Mihailov et al., 2017; Padula, Schaer, Scariati, Maeder, et al., 2017; Scariati et al., 2014; Shashi et al., 2010). Although preliminary, the results of this work indicate that the emergence of psychotic symptoms is associated with a number of structural and functional abnormalities involving the frontal and medial regions (Mancini et al., 2019; Padula, Schaer, Scariati, Maeder, et al., 2017; Padula, Scariati, Schaer, & Eliez, 2018). Finally, grey matter volume in the prefrontal-dorsolateral cortex, cingulate cortex and cerebellum has been shown to be positively correlated with cognitive measures of sustained attention, executive function and verbal memory (Shashi et al., 2010). These structures are therefore important mediators of neurocognition in this population.

These different studies show the extent of brain differences when compared to typically developing individuals and highlights atypical brain maturation relevant for understanding the

link between brain alterations identified with neuroimaging techniques and behavioral observations of cognitive impairment.

4. Cognitive phenotype of 22q11DS

The cognitive profile of individuals with 22q11DS is characterized by low intellectual efficiency (measured by total intelligence quotient, Total IQ), with a mean total IQ shifted 30 points to the left, around 70 (I. M. Campbell et al., 2018; Niarchou et al., 2014; Schneider, Debbané, et al., 2014). In addition, several authors have noted a superiority of verbal performance over non-verbal performance in this population (Furniss, Biswas, Gumber, & Singh, 2011; Zinkstok & Van Amelsvoort, 2005). However, homogeneous and inverted profiles are also observed (Swillen & McDonald-McGinn, 2015).

Independently of the general intellectual level, differences in visual perception are reported in 22q11DS. These include a deficit in visual-motor integration, difficulties in visual perception of shapes and movement, as well as particularities of visual exploration characterized by longer but less frequent fixations on social or non-social stimuli (faces and landscapes) and less time spent on peripheral objects (Bostelmann, Glaser, Zaharia, Eliez, & Schneider, 2017; Duijff et al., 2012; Henry et al., 2002; McCabe, Rich, Loughland, Schall, & Campbell, 2011; Piccini et al., 2017). Together, these findings deserve consideration since they could explain, at least in part, the differences between verbal and non-verbal modality in many domains such as reasoning, memory or attention.

After accounting for intellectual functioning, several cognitive domains also show specific features in 22q11DS. For example, mathematics is an area of relative weakness (compared to reading) with difficulties in understanding and representing numerical quantities (de Smedt, Swillen, Verschaffel, & Ghesquière, 2009; Furniss et al., 2011). However, it was later demonstrated that these deficits could be a consequence of visuo-spatial deficits and highlights

the importance of task selection (Attout, Noël, Vossius, & Rousselle, 2017). Mathematic procedures based on rule learning (reading and writing numbers, calculation procedure) appear relatively preserved but remain less effective (reported as slower) and calculation procedures requiring several steps remain arduous, possibly influenced by other cognitive deficits such as executive functions (Attout et al., 2017; de Smedt et al., 2007). Another feature of 22q11DS is impairment of social cognition, characterized by atypical exploration of faces (more time spent on the mouth), a delay in recognizing the emotion (more clues needed), as well as deficits in taking the perspective of others (Badoud et al., 2017; L. E. Campbell, McCabe, Melville, Strutt, & Schall, 2015; M Franchini et al., 2016; Glaser et al., 2010). Finally, impairments reported in the neuropsychological profile of 22q11DS also include attention, executive functions and memory. In the next paragraphs the currant literature will be reviewed, first on attention and executive functions, then on memory.

4.1. Focus on attention & executive functions

As often described in the context of neurodevelopmental disorders, attention and executive functions (EF) are points of weakness in 22q11DS. First of all, attention deficits are particularly frequent in 22q11DS, since 37-45% of individuals meet the criteria for ADHD and high rates of ADHD in adults (16-35%) suggest a persistence with age (Gothelf et al., 2013; Kates et al., 2019; Schneider, Debbané, et al., 2014; Young et al., 2011). The presentation of ADHD in 22q11DS is slightly different from idiopathic ADHD with higher rates of 22q11DS patients meeting the criteria for inattentive presentation (61-79% in 22q11DS vs. 38-57% in idiopathic ADHD) (Antshel et al., 2007; Niarchou, Martin, Thapar, Owen, & van den Bree, 2015; Schneider, Debbané, et al., 2014; Willcutt, 2012). Moreover, because of the higher expression of the inattentive symptoms, deficits are more difficult to recognize or sometimes attributed to other origins such as low intellectual efficiency or learning disabilities, delaying diagnostic and proper care (Reilly, Senior, & Murtagh, 2015).

In terms of attentional cognitive processes, a study aimed at characterizing the neurocognitive profile of participants with 22q11DS demonstrated a deficit in sustained attention in 26 children and adolescents (Lewandowski, Shashi, Berry, & Kwapil, 2007). Similarly, de Sonneville et al. (2018) found that 58 children and adolescents with 22q11DS scored below the norm on measures of alertness and sustained attention using a computerized battery (Amsterdam Neuropsychological Task). Finally, in a multicentric study of 236 participants diagnosed with 22q11DS aged 6 to 60 years, Morrison et al. (2020) demonstrated a deficit in sustained attention, observable from childhood to adulthood, remaining static over developmental stages. Altogether, maintaining attention over long periods of time seem to be mostly affected in 22q11DS, matching the predominantly inattentive symptoms of ADHD described in the literature. Interestingly, impairment in sustained attention is demonstrated at the group level, independently of a diagnosis of ADHD.

Regarding EF, the profile of 22q11DS is less well defined, probably due to the complexity of this topic. Broadly defined, EF are considered to be a collection of related but distinct higher order abilities that allow us to formulate goals, plan how to achieve them, and carry them out successfully (Anderson & Reidy, 2012; Diamond, 2013; Miyake et al., 2000). When studying EF, two major challenges arise. First of all, although several models have been suggested in the literature, they generally agree on the fact that EF is not a unitary construct (Diamond, 2013; Miyake et al., 2000). EF rather represents an "umbrella" term including multiple sub-domains such as inhibition, updating, shifting or planning. Secondly, EF depend partially on the frontal regions of the brain, whose maturation is protracted (compared to other cognitive function) and extends from childhood into early adulthood (Romine & Reynolds, 2005; Sousa, Amaro, Crego, Gonçalves, & Sampaio, 2018). Additionally, in the general population different sub-domains of EF have been demonstrated to mature at different pace (Akshoomoff et al., 2014; Anderson, 2002; Best & Miller, 2010).

According to this, in the literature on 22q11DS, previous studies have used a wide range of different methodologies and samples, yielding sometimes contradictory findings and an inconclusive overall profile. A recent meta-analysis including 43 papers confirmed a moderate to large EF deficit in 22q11DS (Moberg et al., 2018). More specifically, various isolated components of EFs have been examined in the literature. The authors highlighted deficits in inhibition (McCabe et al., 2014; Shapiro, Wong, & Simon, 2013), working memory (Azuma et al., 2009; Majerus, Van der Linden, Braissand, & Eliez, 2007; Montojo et al., 2014) and more sophisticated skills such as multitasking (Schneider et al., 2016). However, only a few studies have examined different components of EF using different tasks in the same population to refine the profile of deficit. L. E. Campbell et al. (2010) evaluated a broad spectrum of EF components in 50 participants aged 6 to 16 years old with 22q11DS. They highlighted difficulties in finding an alternative solution to a problem (cognitive flexibility), a longer time to initiate problem solving and poorer planning of steps to reach a goal, a shorter verbal span, and poor performance in spatial working memory. Moreover, apart from a slight tendency to premature responses (impulsivity), they did not show any difference in the inhibition tasks compared to the control group. Despite a considerable effort to better describe performance on different executive tasks, a main limitation of this study is that it examines a very wide age range (6 to 16 years). Indeed, because EF develop late and partially depend on the maturation of the frontal areas of the brain (Sousa et al., 2018), skills are at different stages of development when assessed. Although the authors ensured that the average age of the groups was comparable, the effect of age on the results was not taken into account. Shapiro, Tassone, Choudhary, & Simon (2014) describe the development of EF in children and adolescents with 22q11DS aged 7 to 14 years old. The authors evaluated 71 individuals with 22q11DS and 52 healthy controls using different tasks assessing the three components of EFs suggested by Miyake and colleagues: inhibition, updating and flexibility (Miyake et al., 2000). They found lower performance in all

the domains assessed in individuals with 22q11DS, even when controlling for intellectual level. In their study, they also observed atypical trajectories of development of inhibition and cognitive flexibility with age. Conversely, the development of working memory measures seemed to follow the same trajectory as that of the control participants. This study suggests that the development of EF in 22q11DS is relatively complex and not simply related to developmental delay. Indeed, the results indicate that different components of EF have different trajectories, as is also the case in the general population (e.g., Akshoomoff et al., 2014; Anderson, 2002). However, the cross-sectional design of the study as well as the restricted age examined (7 to 14 years) limits the scope of possible conclusions on an actual developmental trajectory of these processes.

Taken together, previous results demonstrate the value of examining multiple components of attention and EF in the same sample to fully grasp the extent of impairment and further delineate the neuropsychological profile. The restricted age range and the cross-sectional design adopted also highlights the necessity for a longitudinal approach in the study of attention and EF in the context of neurodevelopmental disorders such as 22q11DS.

4.2. Focus on memory

Memory deficits have been established as a core cognitive impairment consistently reported in schizophrenia spectrum disorder (Fioravanti, Bianchi, & Cinti, 2012). Preceding the onset of psychotic symptoms and observed throughout the course of the disorder (high risk population, first episode, chronic state, with or without medication), verbal memory deficits have been suggested as a potential predictor of transition to psychosis in at-risk individuals (Valli, Tognin, Fusar-Poli, & Mechelli, 2012). Therefore, memory has been a topic of high interest in 22q11DS research from early on.

Studies exploring memory functioning in 22q11DS have consistently reported impaired non-verbal memory performance, whereas verbal memory appeared to be less affected, or even

preserved compared to intellectual functioning (Bearden et al., 2001; L. E. Campbell et al., 2010; Lajiness-O'Neill et al., 2005). A wide range of tasks have been used to assess memory in 22q11DS, sometimes merging performance of several tasks into a single verbal or non-verbal index, or even a general memory score such as the Children Memory Scale or Wechsler Memory Scale (Cohen, 1997; Wechsler, 1997b, 2010). This approach may be problematic as these tasks recruit a variety of different cognitive processes and thus may blur differential effects (e.g., free recall vs. recognition, associative learning vs. implicit learning, isolated vs. complex stimuli). Comparing performance on multiple non-verbal memory task in 71 children and adolescents, Bostelmann et al. (2016) suggested that the degree of non-verbal memory impairment varies depending on the type of stimuli presented, with greater deficits for more abstract or complex material (e.g., faces or landscape vs. dot localization). Similarly for verbal memory, in a study including 80 children and adolescents with 22q11DS, Woodin et al. (2001) showed significantly higher learning and memory performance with a list of unrelated words (scores in the average range) compared to more complex stimuli such as stories (scores in the borderline range), suggesting rote memory as a relative strength in 22q11DS. Furthermore, Bearden et al. (2001) compared performance using 16 unrelated words (Verbal learning in Wide Range Assessment of Memory Learning, WRAML) and 16 words arranged in 4 semantic categories (California Verbal Learning Test for Children, CVLT-C), but found no significant difference. In light with this, it appears that stimuli presented play a role in the intensity of deficit. Therefore when comparing verbal and non-verbal performance, stimuli should also be similar in difficulty.

Because of its dynamic nature, memory requires multiple sequential processes including acquiring (encoding), storing (consolidation) and retrieving information (Squire & Zola-Morgan, 1991; Thomson & Tulving, 1973). Even though only encoding and retrieval can be measured with standard tasks, memory impairment can occur from failure at any step. In

22q11DS, only few studies have investigated the different components, dissociating encoding from retrieval. Considering the atypical visual perception and exploration patterns characterizing 22q11DS previously mentioned (Bostelmann et al., 2017; McCabe et al., 2011; Piccini et al., 2017), investigating encoding and retrieval processes separately is crucial.

Measuring encoding for non-verbal stimuli, Bostelmann et al. (2017) highlighted impaired encoding on a drawing reproduction task, related to an abnormal pattern of visual exploration measured with the eye-tracking technique. For verbal stimuli, information acquisition is reported to be in the normal range while being slightly lower compared to an age matched control group in children and adolescents with 22q11DS (Albert, Abu-Ramadan, Kates, Fremont, & Antshel, 2018; Debbané, Glaser, & Eliez, 2008; Lewandowski et al., 2007). Finally, Lepach & Petermann (2011) examined verbal and non-verbal learning using parallel task design. The authors observed a progression in the acquisition of new information with repetition in both modalities but demonstrated slower acquisition in the non-verbal task.

With regard to retrieval after a delay, a few studies have reported impairment with non-verbal stimuli. For example Antshel, Peebles et al. (2008) observed lower performance for children and adolescents in a complex drawing task compared to typically developing controls. Similarly, Fiksinski et al. (2019) demonstrated lower performance in immediate and delayed reproduction of 5 drawings in adults. Nevertheless, without controlling for lower encoding performance due to defective visual perception or exploration, conclusions on retrieval are limited. In the verbal modality, since encoding is preserved, the picture is clearer. Several studies have demonstrated preserved verbal memory recall after delays up to thirty minutes (L. E. Campbell et al., 2010; Lajiness-O'Neill et al., 2005). Conversely, reports from patients and caregivers point toward increased forgetfulness and memory loss over time. Standardized tasks available and usually applied for clinical purposes and research, limit the assessment of memory to delays of thirty minutes, yielding only a partial understanding of memory retention and no

information in retrieval after longer delays (days, weeks, months). Limits of the available tasks could explain discrepancies between test performance and patient reports. Finally, in a study investigating forgetting processes (using a directed forgetting paradigm), Debbané et al. (2008) showed that adolescents and young adults with 22q11DS experience difficulty suppressing irrelevant verbal information during retrieval, leading to memory dysfunction. Further investigating of forgetting seems necessary with additional delays in time to better understand the trajectory of forgetting over time and the underlying mechanisms.

5. Specificity of the 22q11DS phenotype

Despite the heterogeneity of the syndrome's manifestations, findings from the literature still suggest a specific profile for 22q11DS, different from other genetic syndromes or idiopathic intellectual disability. For example, a systematic review associated with a trans-diagnostic meta-analysis compared the prevalence of psychiatric disorders in a dozen genetic syndromes including Down syndrome, 22q11DS, fragile X syndrome, Williams syndrome and Prader-Willi syndrome (Glasson et al., 2020). The authors were able to demonstrate a psychiatric phenotype specific to each of the syndromes that does not appear to be caused by intellectual disability. Similarly, Zarchi et al. (2014) compared prevalence of psychiatric disorders and cognitive phenotypes between 22q11DS, Williams syndrome and idiopathic developmental disability. While some parallels were observed (equal prevalence of anxiety, mood disorder and disruptive disorder between groups), 22q11DS stand out with the highest rates of psychotic disorders. Additionally, for neurocognitive measures, both 22q11DS and Williams syndrome showed heterogenous intellectual abilities with lower performance IQ than verbal IQ. These results confirm those of L. E. Campbell et al. (2009) who compared the cognitive profile of children and adolescents with 22q11DS and Williams syndrome. Despite some similarities between these two syndromes, including equivalent verbal skills, the results show better

perceptual reasoning skills in 22q11DS (Performance IQ). Conversely, participants with 22q11DS showed poorer performance on tasks requiring detection of gaze direction, expression of facial emotions and face identification. Quintero, Beaton, Harvey, Ross, & Simon (2014) compared the attentional profile of girls aged 7 to 15 years with 22q11DS, fragile X syndrome and Turner syndrome. They showed that attention disorders were present in each of the diagnoses (compared to a group of typically developing girls) but manifested differently. Girls with fragile X syndrome made more mistakes, suggesting greater impulsivity. Finally, girls with 22q11DS show little improvement in the executive control index with age, suggesting an atypical development of the executive component of attention. In line with these differences between syndromes, Reilly (2012) addresses the issue of etiology related to a patterns of impairment, suggesting specific educational adjustments to consider in the classroom.

In sum, these studies demonstrate that the psychiatric and cognitive profile observed in 22q11DS has some specific features, distinguishable from other genetic syndromes or idiopathic intellectual disability.

6. Medication in 22q11DS

As briefly presented earlier, prevalence of psychopathology in 22q11DS is very high, with 73-79% of individuals presenting with at least one psychiatric diagnosis (Green et al., 2009; Tang et al., 2014). Furthermore, comorbidity of psychiatric diagnosis is also very high with 42-50% of individuals presenting with two or more psychiatric diagnosis and 16% with at least three (Tang et al., 2014; Yi et al., 2015). Because of the increased risk of psychopathology, many 22q11DS carriers are required to take a medication in the course of their lives. However, a large study including 112 individuals with 22q11DS suggest that this population is rather undertreated for their diagnosed psychiatric illnesses (Tang et al., 2014). The authors report that only 42% of individuals with a psychotic disorder are taking antipsychotic medication.

Additionally, 34% of individuals diagnosed with ADHD take stimulants or alpha-2 agonist, and 36% of people diagnosed with mood or anxiety disorder take antidepressants or anxiolytics and 13% take mood stabilizers. It has been suggested that due to medical conditions associated with 22q11DS (e.g., heart defect, hypocalcemia), certain clinicians are reluctant to prescribe medication (Dori, Green, Weizman, & Gothelf, 2017). This is why it is of utmost importance to conduct studies on safety and efficacy of medication in 22q11DS to help guide the care and management of these patients.

Medications most frequently prescribed in 22q11DS include antipsychotics, antidepressants, and stimulants. Paradoxically, studies on the effects of these medications and the short- to long-term outcome are still scarce. In a retrospective study examining 190 records of patients with 22q11DS, Dori et al. (2017) found that treatments with antipsychotics and antidepressants are effective and relatively safe in this population. In a longitudinal study including 62 participants with 22q11DS followed-up 2 to 4 times, Mancini, Maeder et al. (2020) demonstrate that long-term treatment with an antidepressant (Selective Serotonin Reuptake Inhibitor, SSRI) - alone or in combination with atypical antipsychotics - ameliorates cognitive performances (measured by IQ scores) and has a promising effect on brain development (increased volume of dentate gyrus, frontal and cingulate regions).

As for the use of stimulants in 22q11DS, two studies have looked at the effects of methylphenidate (MPH), known under the trade name Ritalin®, Concerta® or Medikinet®, which is the first-line medication for the treatment of ADHD according to Anglo-Saxon recommendations (National Institute for Health and Care Excellence, NICE Guidelines, March 2018). In a first study, Gothelf et al. (2003) evaluated the effects of low dose of MPH (0.3mg/kg) in 12 individuals, aged 5 to 20 years old, with 22q11DS and ADHD. They found that MPH significantly diminished core symptoms of ADHD and improved cognitive measures of attention in a sub-group of 6 participants. In a follow-up after 4 weeks, treatment was shown

to be effective and safe with no significant change in cardiac measures or participants exhibiting psychotic symptoms. Side effects were very common (92%) but never server enough to warrant discontinuation of medication. Similar to other studies on idiopathic ADHD, the most common reported side effect was poor appetite, but other effects were also relatively frequent (irritability, sadness, stomachaches, talking little with others and proneness to crying). In a second study from the same group, the authors evaluated in more detail the effects of MPH on cognition, including working memory, inhibition, mental flexibility and visual attention (Green et al., 2011). The studies included a larger sample (N=34) aged 5 to 20 years old and effects of MPH were compared to a placebo group (respectively N=22 vs. N=12). The results show that a single dose of MPH (0.5 mg/kilo) is associated with an increase in cognitive functions underpinned by the frontal lobes. The authors showed that performance on the cognitive task only taxing working memory was not affected by MPH, while tasks taxing both working memory and inhibition improved significantly with medication, compared to a placebo. After 6 months of regular treatment, the authors re-evaluated the psychiatric diagnosis, observing decrease in core ADHD symptoms of 40%. They also observed that the treatment was well tolerated by the participants (stable side effects) and that cardiovascular side effects were minimal. However, number of participants who continued treatment after the initial dose was small (N=15). Altogether these two studies provide evidence for effectiveness and safety of MPH in 22q11DS. Since they included small sample size, results should be confirmed in a larger sample and long-term effect (chronic users) should be differentiated from short-term effects (single dose). Both studies found encouraging effects both on core ADHD symptoms and associated cognitive measures however, the effect of MPH on specific cognitive measures is still limited with few domains of attention and EF explored.

Finally, omega-3 supplements are also worth mentioning given their safety, tolerability and positive effects reported on cognitive measures of attention (distractibility) in 22q11DS

(Armando et al., 2020). Furthermore, in the sample of 62 patients aged 8-25 years old, individuals with an omega-3 treatment showed less risk of developing an UHR status and lower conversion rate to psychosis. However, results were obtained from an observational analysis and should be confirmed in a randomized clinical trial.

In sum, because of the increased risk for developing psychiatric disorders and the cognitive impairments observed in 22q11DS, medication represents an important aspect of treatment and care of this population. However, as a rare genetic condition, research evaluating benefits of medications specifically for 22q11DS individuals are still scarce with limited number of studies, limited sample size or results derived from observational analysis. This demonstrates the need to conduct more clinical trials in this population.

7. Open questions and thesis objectives

In the previous sections, we have established that 22q11DS has a broad but unique phenotype, clearly distinguishable from other genetic conditions or idiopathic intellectual disability. The singularity of the cognitive profile has also been demonstrated and similarities with cognitive impairments found in other neurodevelopmental disorders (such as schizophrenia or ADHD) are described. In this thesis we focus on two features of the cognitive profile (executive functions and memory) as well as the benefits of a stimulant medication in 22q11DS.

7.1. Extending knowledge on executive function and attention

The literature reviewed in the previous sections clearly point toward impairment of EF and attention in 22q11DS. However, due to the complex nature of EF, with evidence for fractionation (Miyake et al., 2000), one question remains: *is 22q11DS associated with an overall EF impairment, or are some sub-domains of EF more impaired than others?* To answer this question, it appears necessary to explore multiple sub-domains in one sample of participants to get a more accurate picture of the cognitive profile.

Altered brain maturational process of frontal regions during adolescence points toward an atypical developmental trajectory of EF and attention processes (Ramanathan et al., 2017; Schaer et al., 2009). Previous evidence from the literature suggest that the cognitive impairment observed depends both on age and on the domain examined (Morrison et al., 2020; Shapiro et al., 2014). However, results are limited by a cross-sectional approach with either a small age range or using age as a categorical variable. Together, these results demonstrate the necessity to move past group comparisons (22q11DS vs. healthy controls) and instead consider trajectories of maturation of cognitive processes with age from childhood to early adulthood. *How does different sub-domains of EF develop with age? Do they follow similar developmental patterns? Will different tasks, targeting the same cognitive domain, yield different developmental patterns?*

With **Study 1**, the first aim was to to delineate the developmental trajectories with age of multiple EF domains in a longitudinal sample using a broader age range than previous studies. Given the high incidence of psychotic symptoms in 22q11DS, a second aim was to compare the development of EF in participants with/without comorbid psychotic symptoms. Finally, as third aim, association of EF deficits and adaptive functioning was explored. This work is however limited by a small number of cognitive sub-domains explored, yielding only a partial view of the overall developmental profile of EF and attention in 22q11DS.

With **Study 2** the aims were not only to confirm but further extend previous findings on the developmental trajectories of EF and attention in 22q11DS. By exploring additional sub-domains using several tasks per domain in a broader age range, results provide a more reliable overview of patients' cognitive profile. Additionally, the results of this second study also give us the opportunity to reflect on clinical implications for 22q11DS. Indeed, identifying developmental patterns in a specific domain (developmental deficit, lag, deterioration or

maturation) is crucial to set up age-appropriate guidelines and recommendations for evaluation, as well as select appropriate intervention strategies (such as compensation or remediation).

7.2. Extending knowledge on memory

As reviewed earlier, several studies have investigated memory functioning in 22q11DS showing overall a mild impairment of non-verbal memory (possibly influenced by sub-optimal memory acquisition) and relatively preserved verbal memory (L. E. Campbell et al., 2010; Lajiness-O'Neill et al., 2005). However, reports from 22q11DS carriers and their families challenge the general assumption of spared verbal memory, pointing to forgetfulness and memory loss over time. This contrast leads to the following questions: *are the available standardized tests really representative of "long-term" memory performance? Does 22q11DS patients have difficulties remembering after long delays (superior to 30 minutes)?* Furthermore, previous literature specifically measuring forgetting suggests a difficulty suppressing irrelevant verbal information during retrieval, leading to memory dysfunction (Debbané et al., 2008). Thus, open questions are: w*hat kind of tools do we need to investigate patterns of forgetting over time? What does the trajectory of memory retention look like in 22q11DS? And what cognitive mechanisms sustain faster forgetting in this population?*

With **Study 3,** we created a new memory assessment tools to suit our research question enabling us to investigate memory retention over an extended time span (thirty minutes, one day, one week and one month) and study rates of forgetting. The first aim was to investigate memory retention over time in 22q11DS and healthy controls. Due to the deficit reported in visuo-spatial processes, possibly influencing the encoding of visual information, we focused on the verbal modality. The second aim was to determine whether subgroups of patients could be identified based on their verbal memory retention profile. Finally, the third aim was to investigate neural correlates of the behavioral findings. While the results from this study demonstrated faster forgetting in 22q11DS participants (compared to healthy controls), the underlying cognitive

processes responsible for faster forgetting remained unclear. It was suggested that deficient memory consolidation and reconsolidation processes were involved. However, due to the design of the study including multiple retrieval opportunities (four recalls), higher rates of forgetting could result from impaired retrieval of memories or reflect increased sensitivity to interference through reconsolidation processes.

In **Study 4**, we created another version of the task previously used in Study 3, by removing intermediate delays in time, and only keeping retrieval after thirty minutes and one month. The first aim was to examine retrieval without interference of reconsolidation processes. The second aim was to examine the impact of reconsolidation on forgetting rates after a one-month delay by comparing performance in both designs (original design from Study 3 and new design from Study 4).

7.3. Intervention using medication

In the last part of this work, we explore one intervention possibility, namely using stimulant medication to improve EF, attention and memory. As previously mentioned, despite the high prevalence for psychopathology, patients with 22q11DS are rather undertreated for their psychiatric illnesses (Tang et al., 2014). Furthermore, only few studies have investigated the safety and effectiveness (short or long-term) of medication frequently prescribed in 22q11DS leaving clinicians with only limited knowledge. More specifically with regard to stimulant, despite the very high proportion of ADHD observed in 22q11DS and treatment recommendation including stimulants (NICE guidelines, 2018), only two studies have investigated the safety and effectiveness of methylphenidate in 22q11DS. Furthermore, samples were very small and limited cognitive domains were examined. *Therefore, it remains to be investigated if MPH is a valuable medication to consider in 22q11DS? Does MPH improve all cognitive domains or is there a specificity in the effects?*

With **Study 5,** we aimed to investigate the benefit of methylphenidate on core symptoms of ADHD, cognitive measures and daily-life functioning with questionnaires. Compared to previous studies, we explored the effects on a broader range of cognitive measures including attention, EF and memory.

II. EMPIRICAL STUDIES

This section contains the empirical work compiled as a collection of five studies either published in peer reviewed journals, submitted for publication (under review) or in preparation for submission. Inconsistencies in terminology and format or repetitions may occur due to the different journal publishing policies.

Study 1 - Developmental trajectories of executive functions in 22q11.2 deletion syndrome[1]

Abstract

Background: 22q11.2 deletion syndrome (22q11DS) is a genetic disorder associated with a specific cognitive profile. Higher-order cognitive skills like executive functions (EF) are reported as a relative weakness in this population. The present study aimed to delineate the developmental trajectories of multiple EF domains in a longitudinal sample using a broader age range than previous studies. Given the high incidence of psychotic symptoms in 22q11DS, we also compared the development of EF in participants with/without comorbid psychotic symptoms. Given the importance of EF in daily life, the third aim of the study was to characterize the link between EF and adaptive functioning.

Methods: The sample consisted of 95 individuals with 22q11DS and 100 typically developing controls aged 6–26 years. A large proportion of the sample (55.38%) had multiple time points available. Between-group differences in the developmental trajectories of three subdomains of EF (verbal fluency, working memory, and inhibition) were examined using mixed models regression analyses. Analyses were repeated comparing only the 22q11DS group based on the

[1]This study is a reprint of the article: Maeder, J., Schneider, M., Bostelmann, M., Debbané, M., Glaser, B., Menghetti, S., Schaer, S., & Eliez, S. (2016). Developmental trajectories of executive functions in 22q11.2 deletion syndrome. *Journal of Neurodevelopmental Disorders*, 10(8), 1–12. Retrieved from https://doi.org/10.1186/s11689-016-9141-1

presence/absence of psychotic symptoms to investigate the influence of executive dysfunction on the emergence of psychotic symptoms. Hierarchical stepwise regression analyses were also conducted to investigate the predictive value of EF on adaptive functioning.

Results: We observed lower performance on EF domains, as well as atypical development of working memory and verbal fluency. Participants who presented with negative symptoms exhibited different developmental trajectories of inhibition and working memory. Adaptive functioning level was not significantly predicted by EF scores.

Conclusions: The present study highlighted domain-specific atypical trajectories of EF in individuals with 22q11DS and explored the link with psychotic symptoms. However, no relation between EF and adaptive functioning was observed.

Background

Executive functions (EF) can be described as interrelated high-level cognitive processes that play a leading role in formulating goals, planning how to achieve them, and carrying them out successfully (Anderson, 2002; Anderson & Reidy, 2012). In the cognitive literature, there is evidence for the fractionation of EF (Anderson & Reidy, 2012; Diamond, 2013; Miyake et al., 2000). Multiple EF domains are included under the EF umbrella (i.e., initiation of activity, cognitive flexibility, planning, self-regulation, or working memory), all of which play a chief role in day-to-day autonomy and are relevant to most aspects of life (Diamond, 2013). EF emerge early in childhood and continue to develop up to the beginning of adulthood, with each individual domain developing at a different pace (Best & Miller, 2010), making EF a complex topic of study. 22q11.2 deletion syndrome (22q11DS) is a genetic condition, one of the most common multiple anomaly syndromes in humans (Shprintzen, 2008), and is reported to occur in approximately 1 in 4000 live births (Oskarsdóttir et al., 2004). Nevertheless, recent studies suggest that its occurrence could be even higher (Grati et al., 2015). The phenotype

encompasses physical features like heart anomalies, cleft palate, or structural brain anomalies, as well as cognitive and behavioral features, including high rates of psychiatric disorders (Philip & Bassett, 2011; Shprintzen, 2008). A large proportion of affected individuals exhibit early onset psychosis (Schneider, Debbané, et al., 2014), and 22q11DS is associated with increased risk for developing schizophrenia during adulthood (Murphy, Jones, & Owen, 1999). This makes 22q11DS the best homogeneous human model for studying early risk factors and interventions for psychosis (Squarcione et al., 2013). The cognitive profile in 22q11DS is characterized by intellectual functioning (measured by intelligence quotient, IQ) in the borderline range (70–79), with noted deficits in numeracy, visuospatial processing, attention, and multiple executive function domains (Antshel, Fremont, & Kates, 2008; Henry et al., 2002; Squarcione et al., 2013; Woodin et al., 2001). Variability in the cognitive profile can be observed between individuals, as well as within individuals over the years (Philip & Bassett, 2011). For this reason, it appears necessary to study 22q11DS using a developmental approach.

Several studies have investigated EF in 22q11DS (e.g., L. E. Campbell et al., 2010; Chow, Watson, Young, & Bassett, 2006; Lewandowski et al., 2007) in order to characterize the neurocognitive profile in this population. However, the measures used in these studies were generally part of larger batteries examining memory, intelligence, visuospatial processing, or language and were not specific to EF. Although they report EF as a relative weakness in the cognitive profile of individuals with 22q11DS, it is still unclear which domains are more or less affected and how each one develops over time. A few studies have examined a single component of EF to identify specific mechanisms leading to executive impairments. One EF domain, which has received a significant amount of attention in 22q11DS, is inhibition. McCabe et al. (2014) examined pre-pulse inhibition in adolescents and found increased antisaccade errors and a trend toward impaired sensory motor gating, indicating a dysfunction of inhibition pathways in the syndrome. Likewise, Shapiro et al. (2013) detailed the processes

responsible for successful inhibition in children. The authors found that, when compared to controls, reactive inhibition (stopping) was impaired in individuals with 22q11DS, whereas proactive inhibition (anticipatory stopping) was preserved. Azuma et al. (2009) focused on a different EF domain and observed significant spatial working memory deficits in children with 22q11DS. Together, these data highlight specific EF impairments in the syndrome but do not provide any information about the way EF domains develop in 22q11DS.

To our knowledge, only one study to date has assessed several types of EF within the same cross-sectional study of young individuals (7 to 14 years old) with 22q11DS (Shapiro et al., 2014). The results of Shapiro et al. point to deficits in response inhibition, cognitive flexibility, and working memory (both verbal and non-verbal), even after controlling for the influence of intellectual functioning. In addition, the authors identified atypical development of both response inhibition and cognitive flexibility in children with 22q11DS compared to typically developing individuals. Altogether, this study suggests that EF impairments in the syndrome have a complex trajectory and are not simply a by-product of developmental delay. However, because of the cross-sectional nature of the study, the authors did not examine true developmental trajectories of the EF domains, an especially important step in 22q11DS research due the cognitive heterogeneity in the syndrome. Moreover, given the prolonged development of EF and their underlying prefrontal brain regions up to early adulthood (e.g., Romine & Reynolds, 2005), it is interesting to investigate EF in an age range as broad as possible to understand the developmental context for each individual's trajectory. To shed light on these lingering questions, we sought to delineate the developmental trajectories of several EF domains using longitudinal data acquired in a large cohort of individuals with 22q11DS aged 6 to 26 years. Previous studies have shown that differences in developmental trajectories between two groups can be described in different ways: (1) same general shape but the curve is shifted along the age axis, with the peak value attained at a later age; (2) difference in tempo with spurts

at one or several time points; and (3) trajectory lacking shape (Shaw, Gogtay, & Rapoport, 2010).

Research on 22q11DS often focuses on the search of predictive aspects of development to stave off later outcomes. One of the main challenges is to identify, as early as possible, the factors that influence outcome as well as the emergence of psychotic symptoms in order to facilitate the development of specific interventions strategies. Previous studies have shown consistent EF alterations in patients with schizophrenia (Freedman & Brown, 2011). Associations between executive dysfunctions and symptoms of psychosis were also reported in this population, especially with negative symptoms (L. K. Clark, Warman, & Lysaker, 2010; Semkovska, Bédard, Godbout, Limoge, & Stip, 2004). Specifically, significant associations were found between negative symptoms and inhibition (Donohoe, Corvin, & Robertson, 2006). One previous study in 22q11DS also found associations between negative symptoms and multitasking skills (Schneider et al., 2016). However, no longitudinal studies have been conducted on this topic in this population so far.

Initiating behavior at the right time, knowing when to stop oneself, organizing one's day, or planning ahead to be more efficient in different activities are examples of how EF skills are crucial for adaptive behavior in the daily life (Costanzo et al., 2013). Therefore, the third aim of this study was to describe the relationship between different EF domains and measures of adaptive functioning. Often considered as important outcome measures, IQ scores reflect acquired knowledge and test performance, whereas adaptive functioning is often overlooked (Angkustsiri et al., 2012). Closely correlated with IQ, but with higher ecological validity, adaptive functioning measures, such as the Vineland Adaptive Behavior Scales (VABS; Sparrow, 2011), provide information on daily life that can help to gauge a person's autonomy. In contrast to what is observed in typically developing individuals, previous studies showed that IQ was not strongly correlated to adaptive functioning in 22q11DS and that adaptive

functioning scores were usually lower than what is expected considering their intellectual level (Angkustsiri et al., 2012; Dewulf, Noens, & Swillen, 2013). This underscores the importance of examining the cognitive deficits that may alter adaptive functioning in this population.

For the present study, we proposed three main hypotheses: first, we hypothesized that individuals with 22q11DS would perform less well than the control group on all executive domains and that the developmental trajectory of the 22q11DS group would be different from the control group across all domains. Based on previous cross-sectional findings (Shapiro et al., 2014), we expected to find differences not only in terms of delay but also in the shapes of the trajectories (very little evolution with age or early decline). Second, we hypothesized that executive deficits would be involved in the emergence of symptoms of psychosis, especially negative symptoms, and that the developmental trajectories of the executive domains would differ between participants who will present with psychotic symptoms and those who will not. Third, since adaptive functioning depends on executive aspects of cognition (Costanzo et al., 2013), we hypothesized that scores in EF domains would predict adaptive functioning scores in individuals with 22q11DS.

Method

Participants

One hundred ninety-five participants aged 6–26 were recruited as part of a 22q11DS longitudinal study. Ninety-five of them were diagnosed with 22q11DS and 100 were typically developing controls, including siblings (56%) and community controls. The two participant groups were commensurate for gender and age when compared at the first time points but differed on full scale IQ (Table 1). Participants were recruited using advertisements in patient association newsletters and word-of-mouth. The presence of a 22q11.2 deletion was confirmed using quantitative fluorescent polymerase chain reaction (QF-PCR). Written informed consent,

based on protocols approved by the Institutional Review Board of the Department of Psychiatry of the University of Geneva Medical School (Switzerland), was obtained for all participants and their parents (if the participant was younger than 18 years old).

Table 1 Participant characteristics, psychiatric diagnosis and psychotropic medication

		Diagnostic group		Comparison			
		22q11DS	Controls	*t* test	Pearson's Chi-square	ANOVA	p-value
N		95	100				
Gender (male (%))		45 (47.36%)	48 (48%)		0.008		0.930
Age at first time point (mean (SD))		12.80 (4.23)	13.17 (4.43)	0.596			0.552
Full Scale IQ at first time point (mean (SD))		70.71 (12.27)	110.37 (13.62)			454.57	<0.001
VABS outcome measure at last time point (mean (SD))	ABC score	66.73 (12.53)					
	Communication score	71.17 (17.00)					
	Daily living skills score	71.06 (15.22)					
	Socialization score	73.83 (14.51)					
Psychiatric diagnosis (*N* (%))	Simple phobia	42 (44.21%)					
	Attention deficit disorder	36 (37.89%)					
	Generalized anxiety	16 (16.84%)					
	Major depressive episode	13 (13.68%)					
	Psychosis	8 (8.42%)					
	Obsessive-compulsive disorder	7 (7.37%)					
Psychotropic medication total		39 (41.05%)					
Categories	Methylphenidate	26 (66.66%)					
	Antidepressants	12 (30.77%)					
	Antipsychotics	7 (17.95%)					
	Antiepileptic	7 (17.95%)					
	Anxiolytic	3 (7.69%)					

In total, 352 testing time points were acquired, 188 (53.41%) for 22q11DS patients. Longitudinal data (ranging from two to four time points per participant) was available for many participants (55.38%) (Table 2). For participants with at least two time points, the mean interval between consecutive visits was 3.68 years (standard deviation = 0.87). For individuals with only one time point (44.62%), 66 (75.86%) of them either did not have the opportunity to return for a second assessment or dropped out of the study. Twenty-one had additional time points available that were excluded due to missing data (18; 22.45%) or to fit the age range of the study (4; 4.60%).

Table 2 Longitudinal data available per time points

	Number of individuals having at least:				
	1 time point	2 time points	3 time points	4 time points	Total
22q11.2DS	95	59	29	6	189
Controls	100	49	12	3	164
All	195	108	41	9	352

Materials

Cognitive functioning

As part of an ongoing research protocol, participants completed the Wechsler Intelligence Scale for Children (WISC-III) or the Wechsler Adult Intelligence Scale (WAIS-III) to measure general intelligence and reasoning abilities at each time point (Wechsler, 1991, 1997a). Neuropsychological testing included the Conner's Continuous Performance Test (CPT; Conners & MHS Staff, 2000) to evaluate attention and impulsivity, the Stroop task (Albaret & Migliore, 1999) as a measure of inhibition, and the semantic verbal fluency, as a measure of verbal fluency. As we were especially interested in the influence of age on these EF constructs, raw scores were always used. To assess EF, we selected different variables to disentangle the following executive domains: working memory, inhibition (cognitive and motor), and verbal fluency. Working memory was assessed using the Wechsler *Digit Span* subtest, backward part. In this task, participants were asked to repeat backward a gradually increasing set of numbers. Two types of inhibition were investigated: motor and cognitive. In the CPT, participants were instructed to press a button every time a letter appeared on the screen, except for the letter X where participants had to withhold their answer. Several variables are computed based on the participants' performance, and three of them are typically considered as reflecting inhibition processes (Conners & MHS Staff, 2000). The first one is the *commission error score*, which records every time individuals respond erroneously to a non-target. The second one is *hit reaction time score*, defined as mean response time (in milliseconds) for all correct responses. Fast reaction times combined with an unusually high percentage of commission errors can indicate impulsivity. The third score is the *perseveration score*, defined as a response that occurs less than 100 milliseconds after a stimulus. Since perseveration errors can occur for different and often unidentifiable reasons (pre-emptive responding, random responding, or a slow response to the preceding stimulus), we only used the first two scores. To measure the

cost of cognitive inhibition in time, we computed an *inhibition ratio score* by dividing the raw score from the Stroop condition (participants have to name the color of the ink even though the word spells a different color) by the raw score in the color naming condition (participants are instructed to name rectangles of colors as fast as possible). This score reflects the cognitive cost of inhibiting the reading process. A ratio value close to 1 indicates a lesser cost of inhibition. Finally, we assessed verbal fluency using the semantic verbal fluency test, animal category. In this task, participants were asked to name as many animals as possible in 1 minute, without repetitions (e.g., lion, lioness) or proper nouns. This specific category was chosen to ensure that the task difficulty was similar between younger and older participants, since the animal category is not as dependent on reading and writing skills as letter categories. In this task, several variables can be extracted to reflect EF. The first one is the number of word produced, which reflects the capacity to actively search for an answer. The second one is repetitions and perseveration, which are used as an indicator of monitoring and mental flexibility. Variability in the distribution of repetition and perseveration scores was low and strongly deviated from a normal distribution. Therefore, we decided to consider only the number of word produced. This variable is not solely an executive measure and is influenced by lexical level. As a supplementary analysis, we examined the developmental trajectory of a "pure" measure of lexical level, namely the French version of the Peabody Picture Vocabulary Test (PPVT; Dunn, Theriault-Whalen, & Dunn, 1993).

Clinical assessment

All 22q11DS participants and their parents were interviewed separately by a trained psychiatrist using the computerized Diagnostic Interview for Children and Adolescents-Revised (DICA-R; Reich, 2000) and the Structured Clinical Interview for DSM-IV Axis (SCID-I; First, Spitzer, & Williams, 1996). Psychiatric diagnoses and psychotropic medication taken during testing are included in Table 1. Participants who received the same medication at several time points were

only counted once. Information about psychotropic medications was divided in five distinct categories (methylphenidate, antidepressants, antipsychotics, antiepileptic drugs, and anxiolytic medications). Presence/absence of psychotic symptoms at any time of testing was assessed with the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opier, 1967). Both positive and negative symptoms were examined individually using the a priori positive and negative dimensions of the PANSS. For each symptom dimension, the 22q11DS sample was split in two using the following cutoff: participants with at least one item scored 4 or higher (i.e., moderate to severe intensity) were classified as presenting positive/negative symptoms, whereas the remaining participants composed the group with no positive/negative symptoms.

Adaptive functioning

Parents of 89 individuals with 22q11DS (89.47%) were interviewed using the VABS (Sparrow, 2011) to provide information about participants' adaptive behavior. Data were missing for six individuals. For individuals with several time points, we used data from the first time point available. In addition to the Adaptive Behavior Composite score (ABC), the VABS measures three domains of adaptive behavior: communication, daily life functioning, and socialization. Age-appropriate standardized scores were used (mean = 100; standard deviation = 15). For the four individuals older than 18 years old, we used the norms from the upper age level, as suggested in the interview manual.

Statistical Statistical analyses

To quantify developmental trajectories of EF domains in individuals with 22q11DS and typically developing controls, we examined between-group differences using mixed models regression analyses, as described in previous studies by our group (Mutlu et al., 2013; Schneider, Schaer, et al., 2014). This technique allowed us to model the within-subject factor as a nested variable (Dedrick et al., 2009). For each variable, different models (constant, linear,

quadratic, or cubic) were fitted using the *nlmefit* function in MATLAB R2011b (MathWorks). We employed a Bayesian information criterion (BIC)-based model selection method, one of the most powerful model selection methods for mixed models (Peng & Lu, 2012). Statistical significance for the differences in trajectories between groups was assessed using a likelihood ratio test. The outcome of these analyses allows us to either identify shape differences (i.e., curves that do not follow the same path) or intercept differences (i.e., curves that follow a parallel path but not on the same intercept) between the two groups. To ensure that observed differences were not related to intellectual disability, we separated the 22q11DS sample in two groups according to full-scale IQ scores at the first time point ("lower than 70" [N= 46] vs. "higher than 70" [N= 49] groups). We subsequently conducted the same analyses comparing the "higher than 70" group to the controls and the "lower than 70" group to the "higher than 70" group. In order to examine the relationship between psychotic symptoms and EF domains in the 22q11DS group, we compared EF trajectories of individuals who developed psychotic symptoms from those who did not. Both groups were compared using mixed model regression analyses. Positive and negative symptoms were examined separately. Finally, we investigated the predictive value of EF by conducting hierarchical stepwise regression analyses using the VABS composite score or the domain scores as the dependent variable and the EF domain scores as independent variables. To avoid multicollinearity between EF domains, one EF score per domain was selected: Stroop inhibition ratio, digit span backward, and verbal fluency. Full-scale IQ was added in the model in the first step and selected EF scores in the second step. These analyses were performed using SPSS version 22.

Results

Longitudinal analyses

We compared the developmental trajectories of EF in individuals with 22q11DS and controls (Table 3). We observed significant differences in the shape of the groups' trajectories with age for the working memory test ($p<0.004$) and verbal fluency ($p<0.001$). The control group demonstrated consistently higher scores. The intercepts were significantly different for the inhibition measures ($p<0.025$). All tests survived a Benjamini-Hochberg (Thissen, Steinberg, & Kuang, 2002) correction for multiple comparisons ($p<0.025$).

Table 3 Differences in longitudinal trajectories between 22q11DS and controls

		Model fitted	Shape p-value	Intercept p-value
Working Memory	Digit span indirect order	Quadratic	**< 0.001**	n.a.
Inhibition	CPT commission errors	Linear	0.594	**0.025**
	CPT hit reaction time	Quadratic	0.387	**0.020**
	Stroop ratio	Quadratic	0.097	**<0.001**
Verbal fluency	Animals	Linear	**< 0.001**	n.a.
Vocabulary	French Peabody Picture Vocabulary Test	Quadratic	0.087	**<0.001**

Significant values after correction for multiple comparison with Benjamini-Hochberg procedure (i.e., where $p <0.025$) are displayed in **bold**

Most of the curves fitted a quadratic model of change with age (Figure 1). For the 22q11DS groups as well as the control group, both working memory and cognitive inhibition (Stroop ratio) increased during childhood and peaked during early adulthood (18–22 years old), after which point we observed a gradual decrease. The CPT hit reaction time displayed the opposite pattern, with an initial decrease from childhood to early adulthood and then a subsequent increase. Verbal fluency and CPT commission errors fit linear increasing and linear decreasing models of change with age, respectively. Supplementary analyses comparing trajectories of vocabulary performance (French PPVT) with age exhibited no significant difference in terms of shape ($p=0.087$) but a significant difference in terms of intercept ($p<0.001$). These results exhibit a different pattern of development from the verbal fluency task.

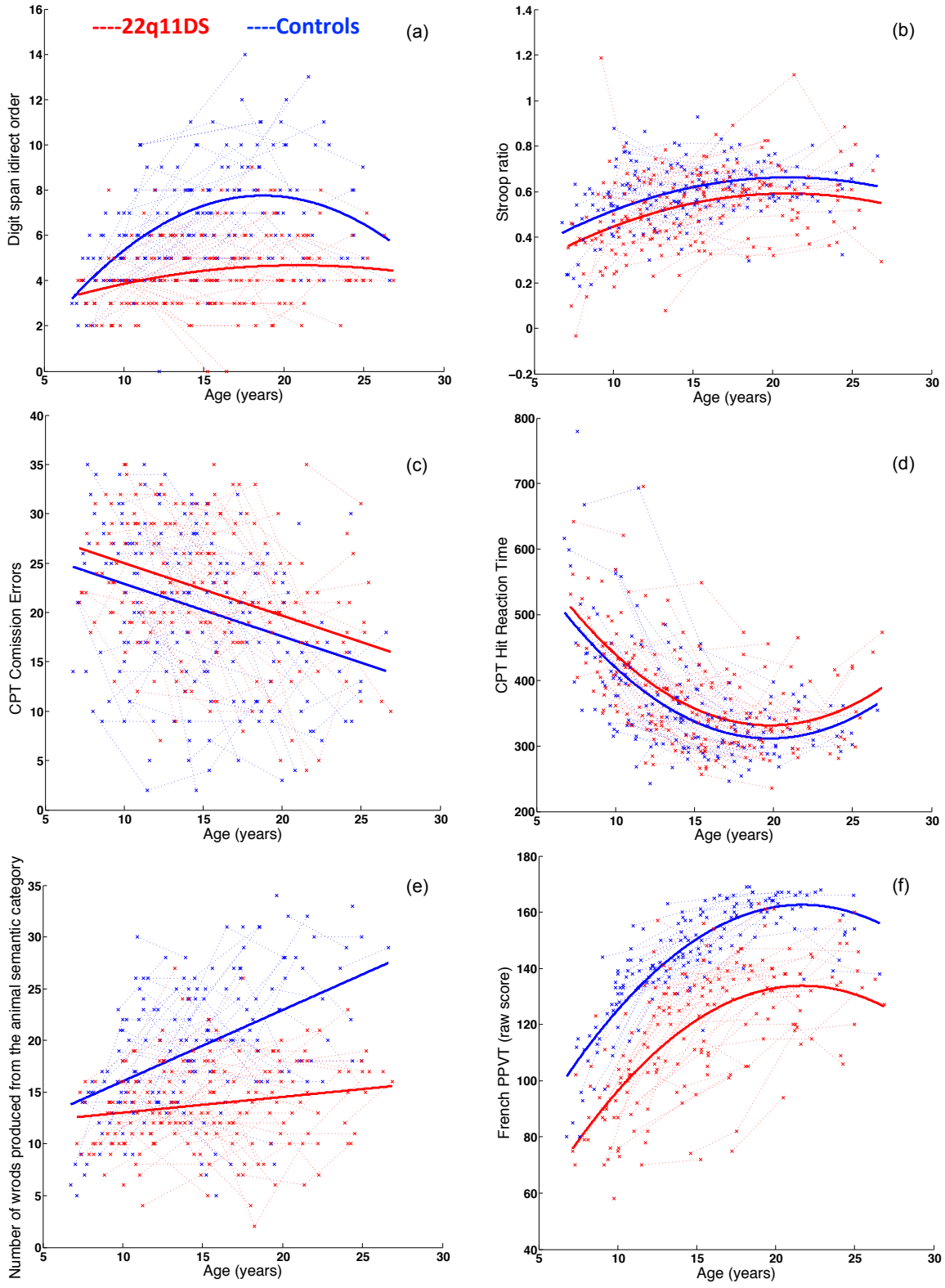

Figure 1 Developmental trajectories of (a) working memory (digit span indirect order), (b) cognitive inhibition (Stroop ratio), (c) motor inhibition (CPT Commission errors), (d) motor inhibition (CPT hit reaction time), (e) verbal fluency (animal fluency), and (f) vocabulary (French PPVT). The data points from a single subject are connected by a dotted line. The solid lines show the model fitted. Data from the 22q11DS group are displayed in *red* and controls are colored in *blue.*

We then removed from the 22q11DS sample all individuals with a full-scale IQ score lower than 70 (see "Statistical Analyses" section) and repeated the mixed model regression analyses on EF variables. After a Benjamini-Hochberg correction ($p<0.016$), the results were comparable to those reported above (see Table 3), except for the CPT measures (commission errors and hit reaction time) which were not statistically different from the controls (Table 4).

Table 4 Differences in longitudinal trajectories between 22q11DS with full-scale IQ higher than 70 and controls

		Model fitted	Shape p-value	Intercept p-value
Working Memory	Digit span indirect order	Quadratic	**0.012**	n.a.
Inhibition	CPT commission errors	Linear	0.607	0.104
	CPT hit reaction time	Quadratic	0.607	0.174
	Stroop ratio	Quadratic	0.023	**0.003**
Verbal fluency	Animals	Linear	**0.001**	n.a.

Significant values after correction for multiple comparison with Benjamini-Hochberg procedure (i.e., where $p<0.016$) are displayed in **bold**

Finally, when compared to each other, the *lower than* 70 group did not significantly differ from the *higher than* 70 group, except on verbal fluency, for which the *higher than* 70 group had a higher intercept ($p=0.001$) in a constant model.

Influence of executive dysfunction on psychotic symptoms

Participants presenting with negative symptoms at any time point showed significant shape differences in the trajectories of the CPT commission errors and digit span indirect order scores compared to participants with- out negative symptoms ($p<0.025$ after the Benjamini- Hochberg correction, see Table 5). The remaining EF variables did not significantly differ between the two groups.

Table 5 Differences in longitudinal trajectories between 22q11DS with negative symptoms and without

		Model fitted	Shape p-value	Intercept p-value
Working Memory	Digit span indirect order	Quadratic	**0.038**	0.710
Inhibition	CPT commission errors	Linear	**0.007**	0.627
	CPT hit reaction time	Quadratic	0.617	0.128
	Stroop ratio	Quadratic	0.440	0.816
Verbal fluency	Animals	Linear	0.668	n.a.

Significant values after correction for multiple comparison with Benjamini-Hochberg procedure (i.e., where $p<0.025$) are displayed in **bold**

On the opposite, participants presenting with positive symptoms at any time point did not differ from those not presenting positive symptoms on any EF measure (see Table 6).

Table 6 Differences in longitudinal trajectories between 22q11DS with positive symptoms and without

		Model fitted	Shape p-value	Intercept p-value
Working Memory	Digit span indirect order	Quadratic	0.448	0.271
Inhibition	CPT commission errors	Linear	0.222	0.580
	CPT hit reaction time	Quadratic	0.792	0.417
	Stroop ratio	Quadratic	0.868	0.675
Verbal fluency	Animals	Linear	0.078	n.a.

Significant values after correction for multiple comparison with Benjamini-Hochberg procedure (i.e., where p <0.025) are displayed in **bold**

Adaptive functioning

Hierarchical multiple regressions controlling for full-scale IQ were used to investigate the links between EF and adaptive functioning. EF did not significantly predict VABS scores (all p>0.05) (see Table 7).

Table 7 Summary from hierarchical multiple regression examining predictive aspects of adaptive functioning scores on executive functioning domains

	Dependent variables				
Steps	Independent variables	R^2	R^2 change	*F* change	*p*
	VABS ABC score				
Step 1	Full scale IQ	0.220	0.220	24.529	**<0.001**
Step 2	Executive domains	0.224	0.004	0.136	0.939
	VABS communication score				
Step 1	Full scale IQ	0.323	0.323	41.506	**<0.001**
Step 2	Executive domains	0.335	0.012	0.514	0.674
	VABS Daily living skills score				
Step 1	Full scale IQ	0.078	0.078	7.387	**0.008**
Step 2	Executive domains	0.960	0.018	0.554	0.647
	VABS Socialization score				
Step 1	Full scale IQ	0.750	0.750	7.083	**0.009**
Step 2	Executive domains	0.101	0.025	0.793	0.501

Significant values are displayed in **bold**

Discussion

The main goals of the present study were to describe executive dysfunction in 22q11DS, to examine developmental patterns in the syndrome compared to controls as well as the influence of psychotic symptoms on these patterns, and to identify the predictive value of EF on adaptive functioning. To achieve these goals, we used multiple measures of EF to describe the development of working memory, inhibition, and verbal fluency in a longitudinal study of 22q11DS individuals and healthy controls ages 6 to 26.

Atypical developmental trajectories of specific EF domains

Lower performance was observed on all EF variables for participants with 22q11DS compared to controls. In the 22q11DS group, atypical developmental trajectories were observed for working memory and verbal fluency, whereas the shape of the inhibition measures' trajectories did not differ between the two populations. These EF impairments are commensurate with previous studies examining working memory and inhibition (Shapiro et al., 2014, 2013). However, to our knowledge, this is the first study reporting verbal fluency alterations in the syndrome.

Development of verbal fluency

In typically developing children, verbal fluency, measured by the number of words produced during a specific time lap, improves with age (Resch, Martens, & Hurks, 2014) until 13 to 15 years old (Anderson, 2002; Hurks et al., 2010). Similarly, in our control sample, we observed a gradual increase in performance on the verbal fluency task, though we did not observe a peak around mid-adolescence (13–15 years). One possible explanation for this difference could be that a group of older controls with very high scores influenced the trajectory of our control group. By contrast, improvement with age in the 22q11DS group was minimal, suggesting that as affected individuals get older, their strategies to successfully initiate and produce words from a semantic category do not progress as quickly as for controls. Interestingly, our sample groups performed similarly on the verbal fluency task during childhood (6–8 years old) before between-group differences became greater with age, a seemingly banal observation that deserves careful consideration given that non-executive aspects (verbal memory disorders or lowered psychomotor speed) can affect verbal fluency (e.g., Tyburski, Sokołowski, Chęć, Pełka-Wysiecka, & Samochowiec, 2015). To ensure that the results reported here are mostly due to executive dysfunction, and not due to a lower lexical level in participants with 22q11DS, we conducted a secondary analysis on vocabulary performances. We observed different

patterns of development for the word fluency task and the vocabulary task. This indicates that even though the lexical level of the 22q11DS group is significantly lower than controls, the developmental path is similar between both groups (see Table 3 and Figure 1).

Trajectories for both groups displayed a gradual increase in raw scores until the age of 20, indicating that the lexical stock in the 22q11DS group increases at the same pace as in the control group. The results observed for the vocabulary task are in contrast with the developmental trajectories obtained for the verbal fluency task, which exhibited a significant difference in shape. As displayed in Figure 1, there was only a minimal improvement with age in the 22q11DS group. This implies that even though their lexical stock increases with age, the number of words correctly produced during the verbal fluency test remains (approximately) identical. Altogether, this analysis suggests that the atypical trajectory observed for the verbal fluency task reflects, at least partially, an executive dysfunction even though it is not a pure executive measure. A qualitative analysis of the productions (i.e., clustering of words, switch between clusters) would be an informative addition to future studies (Hurks et al., 2010; Sauzéon, Lestage, Raboutet, N'Kaoua, & Claverie, 2004).

Development of working memory

Verbal working memory, measured by a number repetition task (backward digit span), is another EF domain explored longitudinally in the present study. Our participant groups differed in the shape of their development on verbal working memory measures, indicating that this domain develops atypically in 22q11DS compared to controls. However, similar to the verbal fluency results, while the younger children (6–8 years old) were not especially different from the controls, participants with 22q11DS tended to reach a developmental plateau much faster than controls. These results contrast with previous findings suggesting that working memory develops typically within the syndrome (i.e., weaker performance but same progression as in the control group) (Shapiro et al., 2014). This difference may be related to two important

methodological discrepancies with Shapiro et al.'s study. First, the limited age range in the previous study (7 to 14 years old) may have made it difficult to observe changes occurring later in life. This is in accordance with our result that younger children with 22q11DS performed similarly to their typically developing peers on working memory tasks. Without the inclusion of older adolescents and adults in our sample, we would not have observed a developmental plateau in working memory. Second, Shapiro et al. adopted a cross-sectional design, which may have prevented the detection of atypical developmental trajectories in the 22q11DS group.

Development of inhibition

The final EF domain investigated in the present study was inhibition, which was evaluated using measures of the cognitive cost of inhibition (Stroop ratio) and impulse control (CPT commission errors and hit reaction time). The performance of 22q11DS participants on the inhibition measures exhibited a shape resembling that of controls, despite the fact that the 22q11DS group's scores were significantly lower than those of the controls (i.e., significant intercept difference). Specifically, the pattern emerging from our analyses depicted an increase in inhibition capacities with age in 22q11DS, echoing what is observed in the control group. These results are in contradiction with previous findings reporting atypical developmental of inhibition in 22q11DS (Shapiro et al., 2014). However, the methodological differences between the two studies (age range, task differences, longitudinal design) may, once again, account for these discrepancies. The same group of authors published a previous study examining the development of inhibition using a task that differentiated be- tween the processes underlying response inhibition (proactive, reactive) (Shapiro et al., 2013). The authors reported significant differences between these processes suggesting that the mechanisms underlying inhibition might be affected unevenly in the syndrome. In light of these previous findings, it may be that our tasks tap different underlying con- structs than the tasks used by Shapiro et al. Future studies examining the different components of inhibition longitudinally would help explain these

discrepancies. In summary, our first hypothesis was only partially supported. 22q11DS individuals were impaired on all three EF domains compared to controls but exhibited atypical development on only two of those domains (working memory and verbal fluency).

Role of intellectual disability on EF measures

Post hoc analyses allowed us to disentangle the influence of intellectual disability on EF tasks in the present study. Even when individuals meeting the criterion for intellectual disability (full-scale IQ lower than 70 points) were removed from the 22q11DS sample, the trajectories of working memory, verbal fluency, and cognitive inhibition remained unchanged. This indicates that the different developmental trajectories (differences in shape) of working memory and verbal fluency between 22q11DS and controls are not only a by-product of intellectual disability. Furthermore, the intercept difference for the cognitive inhibition measure indicates a specific deficit rather than a consequence of intellectual disability. On the other hand, the developmental trajectory of motor inhibition (CPT commission errors and hit reaction time) no longer differed between the two groups, after the exclusion of individuals with intellectual disability. This lack of difference indicates that individuals affected by 22q11DS with an IQ higher than 70 have comparable motor inhibition than controls and that the subgroup with an IQ below 70 was probably driving the observation of poor impulse control. Interestingly, when compared against each other, the 22q11DS subgroups did not significantly differ on EF measures, except for verbal fluency. A possible explanation for this result is that, as already mentioned before, verbal fluency is greatly influenced by non-executive functions that are also measured in IQ scales (e.g., vocabulary). Nevertheless, the fact that the higher than 70 subgroup performed differently than controls indicates that verbal fluency is impaired in 22q11DS.

Relationship between executive dysfunctions and psychotic symptomatology

By comparing trajectories of individuals who displayed psychotic symptoms at any time point to those who did not, we found a link between certain executive domains and negative

symptoms. Specifically, both for inhibition and working memory, performance of individuals with or without psychotic symptoms were very similar in childhood. However, improvement of these two processes with age was minimal for individuals with negative symptoms, whereas the group without symptoms improved significantly and regularly. These results seem to indicate that EF dysfunction exists prior to the onset of negative symptoms. On the opposite, no association was found with positive symptoms. Hereby, we replicated that EF dysfunctions are specifically associated with the emergence of negative symptoms, whereas they are independent of positive symptoms in patients with schizophrenia (Donohoe et al., 2006; Semkovska et al., 2004). Also, these results are in line with a previous study by our group in 22q11DS, showing that negative symptoms were associated with deficits in multitasking skills (Schneider et al., 2016). In the present study, specific associations were found with the inhibition and working memory domains, which are involved in maintaining goals in memory and purposely implementing them at the right moment (e.g., in resisting dominant action scheme). It suggests that these processes could underlie the development of negative symptoms and is in accordance with previous conceptualizations of negative symptoms as a "pathology" of goal-directed behavior (Brown & Pluck, 2000). However, this hypothesis should be further examined, and these results need to be interpreted with caution since only a few aspects of EF were examined in the present study. In fact, positive symptoms could be influenced by an atypical development of other executive domains not considered in the scope of this article.

EF and adaptive functioning

Contrary to our second hypothesis, we found no relationship between EF measures and adaptive functioning scores. It is possible that the absence of significant relationship is at least partially explained by our choice of EF tasks. Indeed, difficulties experienced in a test situation are not directly related to difficulties observed in the real world, such as those assessed in the VABS inventory (Burgess, Alderman, Evans, Emslie, & Wilson, 1998). Furthermore, examining only

one process at the time, in a controlled experimental setting, free from distraction, may not be representative of day-to-day tasks that require the simultaneous use of several EF domains. For this reason, questionnaires targeting behavioral aspects of EF in a naturalistic context (i.e., Behavior Rating Inventory of Executive Functions, BRIEF) are usually poorly related to cognitive measures of EF in different clinical populations (Gioia, Isquith, Guy, & Kenworthy, 2000; Ritter, Perrig, Steinlin, & Everts, 2014). In the field of 22q11DS, our group previously showed that poor multitasking abilities, as measured during a naturalistic experimental paradigm, were significantly associated with the VABS daily living skills domain (Schneider et al., 2016). Indeed, failure to multitask effectively may be a bigger hindrance to functional impairment than intellectual disability. These results indicate that to fully understand EF deficits in 22q11DS and to develop targeted interventions, it is necessary to use multiple measures with ecological validity to target core aspects of EF (i.e., inhibition, updating, cognitive flexibility).

Limits, future directions, and clinical implications

Our work is not without critical limitations. First of all, the EF tasks used in the present study were selected retrospectively from a large longitudinal dataset. The chosen EF tasks involve other aspects of cognition and are not "pure" measures of EF. For example, working memory was only evaluated on its verbal component, whereas the visuospatial component is also very import- ant. Furthermore, data on significant aspects of EF, such as cognitive flexibility or planning skills, were not available longitudinally, despite the fact that they are reported as weaknesses in this syndrome (L. E. Campbell et al., 2010; Shapiro et al., 2014). Given that two out of the three investigated domains showed atypical development, other domains could be affected too. Future research should focus on collecting longitudinal data on a larger sample of tasks that specifically target and isolate EF domains. Furthermore, it would be important to integrate measures or questionnaires with ecological validity to truly capture the executive

profile of this specific population. Finally, as illustrated in the current study, a great variability between individuals with 22q11DS was observed on the executive tasks. This heterogeneity begs the question of how to identify and characterize subgroups within the 22q11DS population. Future research should investigate this aspect in order to create more specific interventions.

Clinical implications of the results presented here are various. First of all, the data reported in this paper suggest that young children with 22q11DS (6–8 years old) have comparable performance to controls in some executive domains, but the gap between both groups widens progressively during adolescence. Furthermore, different executive domains do not display similar developmental patterns. Therefore, regular comprehensive neuropsychological assessments of EF should be conducted with individuals affected by 22q11DS to identify specific impairments. Secondly, if executive dysfunction is highlighted, specific interventions as well as environmental improvements could be implemented (e.g., planning and organization flowcharts, minimizing environmental interferences, break down information in small chunks). Finally, it remains to be examined whether cognitive remediation programs performed during childhood and focusing on EF have a beneficial impact on the development of EF later in life.

Conclusions

In conclusion, we investigated the developmental trajectories of three executive domains in a large longitudinal cohort of individuals affected by 22q11DS and controls aged 6 to 26 years. We identified significantly lower performance on all three executive domains and atypical development of verbal working memory and verbal fluency in 22q11DS. Deficits in specific domains were related to future development of negative symptoms, but not positive. We further tested the predictive value of EF domains on adaptive functioning but observed no significant association.

Study 2 - Age-related improvements in executive functions and focal attention in 22q11.2 deletion syndrome vary across domain and task[2]

Abstract

Objective: Executive functions (EF) and focal attention have been identified as a weakness in the profile of 22q11.2 deletion syndrome (22q11DS). However, due to a high variety of tasks used across studies, the current literature does not allow to conclude whether impairment may be more pronounced for specific sub-domains of EF and focal attention. Furthermore, age-related changes have only been examined in a few studies, so far only yielding a partial view of the overall developmental profile.

Method: In a broad age range (8-35 years old) composed of longitudinal data, 183 participants (103 diagnosed with 22q11DS) completed an extensive assessment of executive function and attention. To get a more complete overall vision of specific versus global impairments, multiple domains with several tasks per domain were examined.

Results: Results suggest that differential impairments and trajectories depend on the specific sub-domains. In detail, compared to healthy controls, individuals with 22q11DS not only had lower overall inhibition skills, but our findings show that their initiation skills developed at a slower pace than healthy controls. Results are less clear regarding cognitive flexibility, updating and focal attention, for which performance strongly depended on the task that was selected to assess the domain.

Conclusions: Findings confirm and extend knowledge on differential developmental patterns of EF and attention domains in 22q11DS. They further stress the necessity to administer extensive, multi-facetted evaluations to have a more reliable overview of patients' cognitive profile.

[2] This study is a reprint of the article: Maeder, J., Zuber, S., Schneider, M., Kliegel, M., & Eliez, S. (under review). Age-related improvements in executive functions and focal attention in 22q11.2 deletion syndrome vary across domain and task

Introduction

Chromosome 22q11.2 deletion syndrome (22q11DS) is a genetic condition affecting multiple systems, including the brain, resulting in a specific neuropsychological profile (McDonald-McGinn et al., 2015). Among the different cognitive domains that show deficits, one of the key abilities affected is executive functions (EF). Playing a leading role in formulating goals, planning how to achieve them, and carrying them out successfully, EF importantly contributes to academic and professional success, as well as autonomy in daily-life (Anderson & Reidy, 2012; Diamond, 2013). More specifically, performance of 22q11DS individuals on EF measures in childhood predict adaptive behavior and social adjustment in young adulthood (Albert et al., 2018).

For over two decades, deficits in EF and attention have been studied in 22q11DS. A recent meta-analysis reported a moderate to large EF impairment in 22q11DS (Moberg et al., 2018). Similarly, deficits in EF are supported by neuroimaging studies showing structural and functional alterations of frontal regions (typically underlying EF) that correlate to task performance (Da Silva Alves et al., 2011; Harrell et al., 2017; Padula, Schaer, Scariati, Maeder, et al., 2017; Rogdaki et al., 2020; Scariati et al., 2016; Shashi et al., 2010). Yet, previous studies have used a wide range of different methodologies and samples, yielding sometimes contradictory findings and an inconclusive overall profile. Furthermore, the current literature does not allow to conclude whether 22q11DS is associated with an overall EF impairment, or whether impairments may be more pronounced for specific sub-domains of EF. This is mainly due to two methodological shortcomings regarding task selection and developmental trajectories of EF.

Despite the recognized diversity of EF models (Karr et al., 2018; Miyake et al., 2000), early studies aiming to describe the neuropsychological profile of 22q11DS have considered EF as a unitary construct and thus have assessed the participants' overall executive functioning with

only one or two global EF measures such as Wisconsin Card Sorting Test or Trail-Making Test (Lewandowski et al., 2007; Woodin et al., 2001). In contrast to examining overall executive functioning, later studies focused on one specific executive domain at a time, such as inhibition, working memory or multitasking (Kates et al., 2007; Majerus et al., 2007; McCabe et al., 2014; Montojo et al., 2014; Schneider et al., 2016; Shapiro et al., 2013). These studies contributed important information on certain executive processes that are impaired in 22q11DS. However, in order to achieve a more fine-grained understanding of EF and attentional profile in this particular population, multiple executive domains need to be assessed simultaneously in the same sample. In that context, it should be noted that a major difficulty regarding research on EF is task impurity, since tests designed to measure EF recruit both executive and non-executive abilities. The use of different measures across studies to assess the same construct could contribute to explain the observed differences, and this issue could be solved by the use of several tasks assessing the same executive domain in the same sample, which so far has never been done in this population.

Moreover, in terms of developmental processes, most previous studies did not consider age as an important factor, and thus separately focused either on children and adolescent populations or on adults (L. E. Campbell et al., 2010; Chow et al., 2006; Henry et al., 2002). However, studies conducted in the general population show that both EF and attention partially rely on the frontal regions of the brain, whose maturation extends into early adulthood (Sousa et al., 2018). Additionally, excessive cortical thinning of frontal regions during adolescence has been demonstrated in 22q11DS, which might point toward an atypical developmental trajectory of EF linked to altered brain maturational process in this population (Ramanathan et al., 2017; Schaer et al., 2009). Thus, to fully apprehend the development of EF in 22q11DS, studies should widen the examined age-range from childhood across adolescents to (early) adulthood. Unfortunately, as highlighted in Morrison et al. (2020), the literature on the cognitive

trajectories from childhood to adulthood in 22q11DS is still scarce and inconsistent. One of the few studies addressing this issue, examined performance of 236 participants with 22q11DS aged between 6-60 years old (Morrison et al., 2020). They showed that the magnitude of impairment differed by developmental stage (i.e., how old patients are) but also by the specific cognitive domain that is examined. More specifically, processing speed seemed to be more impaired in children, whereas working memory was more impaired in adults, and sustained attention was altered across age groups. Although this study provides important insights into developmental differences between age groups, it considered age as a categorical variable, based on the definitions of "childhood", "adolescence" and "adulthood" of the World Health Organization guidelines (https://www.who.int). However, EF and attention mature in a non-linear dynamic way, with different domains showing different trajectories over time (Akshoomoff et al., 2014; Anderson, 2002; Romine & Reynolds, 2005; Waber et al., 2007). According to this, to avoid reducing the data to age-group differences and to fully grasp the dynamic of the different trajectories, age should be considered as a continuous variable. To our knowledge, only a few of studies on 22q11DS have examined continuous age-related trajectories of EF and attention, while also assessing multiple executive domains. One study showed a lack of improvement of inhibition and cognitive flexibility performance with age (Shapiro et al., 2014). However, there was a significant effect of age on working memory (verbal and non-verbal) performance, with older participants exhibiting a higher working memory span. Another study found that executive control of attention is affected by age, with younger children having more pronounced impairments and more variable scores (Stoddard, Beckett, & Simon, 2011). However, both studies are limited by a cross-sectional design that does not allow to take individual variability into account, and a small age range from 7 to 14 years old, thereby yielding only a partial view of the full childhood-to-adulthood trajectory. A third study examined neurocognitive changes over a 3.5 years interval in children and

adolescents (Hooper et al., 2013). They reported significantly lower performance in the 22q11DS group compared to healthy controls for intellectual functioning, attention, cognitive flexibility, working memory and processing speed at first and second evaluation. When controlled for chronological age, changes in raw scores over time between evaluations was significantly different only for one measure of sustained attention with slower gain for 22q11DS participants. Furthermore, in terms of developmental patterns (for a visualization, see Figure 1), a study discussing the use of raw scores found that most measures of reasoning (verbal and non-verbal), EF (planning, set-shifting, spatial working memory) and attention follow a developmental deficits model (i.e., static cognitive impairment that emerges early in development and remains stable) (Chawner et al., 2017).

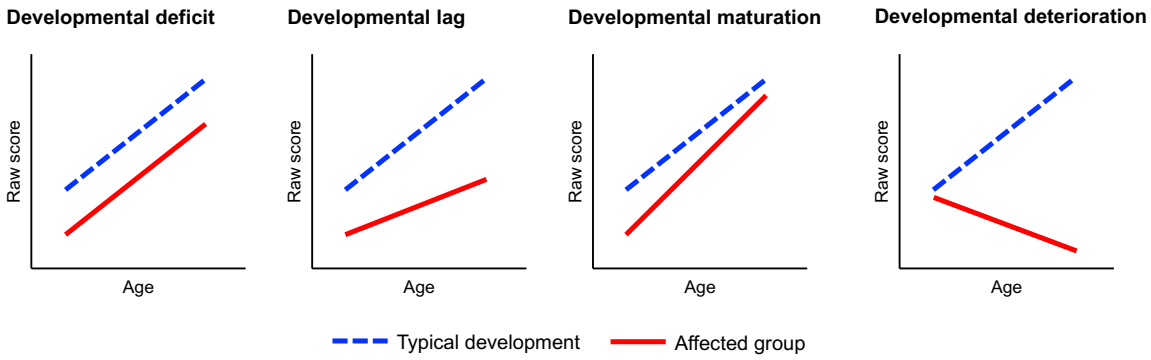

Figure 1 Visualization of four developmental patterns of raw scores with age (Adapted from Chawner et al., 2017)

Only one measure of non-verbal reasoning (block design) showed a development lag pattern (i.e., growth in absolute ability, but growth that lags behind the control group) and one measure of processing speed yielded a developmental maturation pattern (i.e., initial cognitive impairment but development catches up with control group later on). No developmental deterioration (i.e., decline in absolute ability) was observed. Even though a longitudinal design was adopted (two visits with a mean 2.7 year gap), the age range was still limited in this study (mean age visit 1 = 9.9, standard deviation = 2.4; mean age visit 2 = 12.5, standard deviation =

2.3). Finally, a previous study from our group highlighted deviant trajectories of updating (small improvement with age in the 22q11DS group with individuals reaching a developmental plateau much faster than controls) and verbal fluency (very modest improvement with age in the 22q11DS group compared to controls) with age, compared to a control group in a large sample of individuals aged 6-26 years old (Maeder et al., 2016). On the opposite, the trajectory of inhibition followed the same pace as the control group, even if performances were overall significantly weaker in 22q11DS. The major limitation of this study was that only a few domains in EF were examined, again, yielding only a partial view of the overall developmental profile of EF and attention in 22q11DS.

Taken together, the available literature shows evidence for different patterns of development depending on the cognitive domain or task examined but is limited by the age range examined and the selection of cognitive domains in the same sample of participants. Thus, the present study aims to not only confirm but further extend previous findings on the developmental trajectories of EF and attention in 22q11DS. Identifying developmental patterns in a specific domain (developmental deficit, lag, deterioration or maturation) is crucial to set up age-appropriate guidelines and recommendations for evaluation, as well as select appropriate intervention strategies (such as compensation or remediation).

Compared to the existing literature, this work extends the current knowledge on two major points. First of all, a wider range of cognitive domains in the same sample is examined and with an age-matched control group. We aimed to explore if 22q11DS patients would perform worse than controls on all EF and attention or if some domains are less affected, yielding no group difference. Furthermore, to target the issue of impurity, each domain was examined using at least two different tasks. For a domain to be considered as truly impaired, we expect that multiple tasks in the same domain will yield converging results. Otherwise, group differences could be related to specific aspects to the task (e.g., speed, visual or motor skills).

Secondly, participants were examined in a wide age range (8 to 35 years), considering age as a continuous variable and using raw scores to fully observe developmental patterns. We hypothesized that overall, we would observe an effect of age on all variables showing improvement in raw performance with age. We expect results to show either developmental deficit of lag, demonstrated by linear or quadratic trajectories. More specifically, based on previous literature, we expect developmental lag for verbal and non-verbal updating and initiation processes (Maeder et al., 2016; Morrison et al., 2020; Shapiro et al., 2014, 2013). We hypothesize that inhibition will show developmental deficit, as well as visual attention (Chawner et al., 2017; Hooper et al., 2013; Stoddard et al., 2011). Finally, for cognitive flexibility, previous results are less clear but lead us to except either developmental lag or deficit (Chawner et al., 2017; Hooper et al., 2013; Shapiro et al., 2014).

Method

Participants

One hundred and eighty-three participants, were recruited as part of a longitudinal study on 22q11DS (Geneva cohort) (Maeder et al., 2016; e.g., Schaer et al., 2009). One hundred and three (56.28%) were 22q11.2 deletion carriers. The age ranged from 8 to 35 years old. All participants completed an extensive assessment several tasks of EF and attention, including visual focal attention, inhibition, flexibility, updating and initiation (see description in Supplementary material, Table S1). Due to the longitudinal design of the cohort, half of all participant (49.18%) were common to a previous study (Maeder et al., 2016) although assessed at an older age and with a wider task set (only 4 similar tasks).

The presence of the deletion was confirmed using quantitative fluorescent polymerase chain reaction (QF-PCR). The control group was composed of siblings of the affected participants (80%) and community controls. Participants of the two groups did not differ in terms of age or

gender distribution (see Table 1). All participants were recruited through advertisement in patient association reunions, newsletters and word-of-mouth. Written informed consent, based on protocols approved by the Swiss Ethical Committee of Geneva (CCER, Switzerland), was obtained for all participants and their parents (if the participant was younger than 18 years old). A trained psychiatrist (SE) interviewed all participants with 22q11DS and their caregivers using the computerized Diagnostic Interview for Children and Adolescents-Revised (DICA-R; Reich, 2000) or the Structured Clinical Interview for DSM-IV Axis I (SCID-I; First et al., 1996). Psychotic disorders and psychotic symptoms were assessed with the supplement of the Schedule for Affective Disorders and Schizophrenia for School-age children Present and Lifetime (K-SADS-PL; Kaufman et al., 1997). At time of testing, 66 (64.08%) of the participants with 22q11DS had at least one psychiatric diagnosis and 46 (44.66%) were taking medication that can affect cognitive performance (see Table 1). Typically developing controls were screened for psychiatric illnesses and medication prior to inclusion in the study.

Materials

Assessment of executive function and attention

Tasks were chosen to evaluate different aspects of attention and executive function (visual attention, inhibition, flexibility, updating and initiation) in different modalities (verbal and non-verbal) and with different types of tools (paper/pencil and computerized tasks). From the eleven tasks examined, three were selected from the computer-interfaced Cambridge Neuropsychological Test Automated Battery (CANTAB). Tests were administered using the CANTABeclipse version 6, on a portable touch-screen tablet running on a Windows-based PC system.

Table 1 Participant characteristics

			Diagnostic group		Comparison		
			22q11DS	Controls	ANOVA	Pearson's Chi-square	p-value
Cross-sectional N			103	80			
Longitudinal N			32	20			
Time points with all tasks complete (%)			114 (84.44%)	82 (82.00%)			
Gender (male (%))			53 (51.5%)	35(43.8%)		1.071	0.301
Age at first timepoint (mean (SD))			16.72(5.84)	15.68 (5.63)	1.476		0.226
Full Scale IQ at first time point (mean (SD))			72.26 (13.74)	112.71(13.62)	389.778		**<0.001**
Psychiatric diagnosis (%)	Total		66(64.08%)				
	Categories	Psychosis	10(9.71%)				
		Attention deficit disorder	28(27.18%)				
		Simple phobia	29(28.16%)				
		Social phobia	5(4.85%)				
		Generalized anxiety disorder	20(19.42%)				
		Separation anxiety disorder	3(2.91%)				
		Major depressive episode	9(8.74%)				
		Obsessive-compulsive disorder	4(3.88%)				
		Oppositional defiant Disorder	3(2.91%)				
Medication (%)	Total		46(44.66%)				
	Categories	Methylphenidate	19(18.45%)				
		Antidepressants	23(22.33%)				
		Antipsychotics	20(19.42%)				
		Antiepileptic	6(5.83%)				
		Anxiolytics	4(3.88%)				

Significant values at the 0.05 level are displayed in **bold**
NB: Participants who had the same diagnosis or received the same medication at several time points were only counted once

Detailed descriptions of the tasks can be found on the CANTAB website (https://www.cambridgecognition.com). As shown in Table 1, all the tasks were completed for 196 (83.40%) timepoints. Specific task description can be found in Supplementary material 1.

Intellectual functioning

Intellectual functioning was assessed using the Wechsler intelligence scale for children (6-16 years old) or adults (17 and up) (Wechsler, 1997a, 2004, 2011, 2016). Due to the longitudinal design of this study, different versions of the test battery were used. Therefore, only the full-scale intellectual quotient (FSIQ) is reported and not the other subscales. FSIQ at first time point was missing for two participants (both with 22q11DS) for whom only data on executive function and attention was collected.

Statistical analyses

For population description, diagnostic groups were compared on age, gender and baseline FSIQ using SPSS 25 (IBM). Trajectories of performance with age were examined using mixed model regression analyses in MATLAB R2018b (Mathworks), already reported in previous studies

(Maeder et al., 2016; Mancini et al., 2019). This analysis allows to examine the trajectory with age of a given variable by identifying group differences (i.e., trajectories that follow a parallel path but not on the same intercept) and interaction with age (i.e., trajectories that do not follow the same path). To fully grasp the pattern of development with age, raw scores are used in the analysis. As sometimes different versions of tests were pooled together, the test version was included as a covariate when appropriate (Conners' Continuous Performance Test, Color Trail Test, Wechsler batteries).

Results

Comparison of developmental trajectories between 22q11DS and healthy controls

Regarding the developmental trajectories, almost all of the examined variables fitted either a linear or a quadratic model, suggesting an effect of age on the majority of the domains (see Table 2 for details). Only two measures of flexibility, one measure of inhibition and some supplementary measures from updating fitted constant models best.

Table 2 Results from the mixed model analyses, group comparison (22q11DS vs. Controls)

Domain	Variable	22q11DS vs. Controls		
		Model order	group effect p-value	interaction p-value
Visual attention	CPT Omission errors %	linear	**0.002**	0.958
	CTT Adjusted time part A	quadratic	**<0.001**	0.416
	Number of symbols	quadratic	**<0.001**	**<0.001**
Inhibition	Stroop inhibition ratio	quadratic	**0.013**	0.921
	CPT Commission errors %	linear	**0.040**	0.236
	SST SSRT	constant	0.223	n.a.
Flexibility	CTT flexibility ratio	constant	0.092	n.a.
	IED EDS errors	constant	**<0.001**	n.a.
Updating	Backward span	quadratic	**<0.001**	**0.041**
	Letter-number span	linear	**<0.001**	0.481
	SWM Total between errors	linear	**<0.001**	0.075
	SWM between errors 4 blocks	constant	**<0.001**	n.a.
	SWM between errors 6 blocks	constant	**<0.001**	n.a.
	SWM between errors 8 blocks	linear	**<0.001**	**0.025**
Initiation	Number of animals	linear	**<0.001**	**<0.001**
	Number of designs	quadratic	**<0.001**	**0.007**

Significant values at the 0.05 level are displayed in **bold**

Regarding group comparison, for visual focal attention, a significant difference between groups was observed for all measures, with lower performance in the 22q11DS group for *Conners' Continuous Performance Test omission error %* (p=0.002), *Color Trails Test Adjusted time*

part A (p<0.001) and *Number of symbols* (p<0.001). Only the latter displayed a significant interaction with age (p<0.001), with 22q11DS participants improving less with age and reaching a plateau earlier than the control group (for a visual representation of the different trajectories, see Figure 2).

Inhibition showed mixed results depending on the studied variable. Both cognitive inhibition (measured by the *Stroop inhibition ratio*) and motor inhibition (measured by *Conners' Continuous Performance Test commission error %*) yielded significant group differences in favour of the control group (respectively: p=0.013 and p=0.040). Nevertheless, trajectories with age were similar across groups. No group difference was observed for *Stop Signal Reaction Time* (p=0.223).

For flexibility measures, a significant group difference was only found in *Extra Dimensional Shift Errors* from the Intra-/Extra-Dimensional Shift task, with higher rates of errors for the 22q11DS group (p<0.001). The *Color Trails Test Flexibility ratio* showed comparable performance between groups (p=0.092).

For updating, both verbal and non-verbal performance were significantly poorer in the 22q11DS group (p<0.001). Only the *Backward span* displayed significant interaction with age (p=0.041), with a smaller performance increase with age in the 22q11 group. Interaction with age was not significant for *Letter-number span* (p=0.481) and *Spatial Working Memory Total between errors* only reached trend level (p=0.075). *Post-hoc* analyses on the Spatial working memory task separating results according to the working memory load showed a significant interaction with age (p=0.025) at the highest load (*Between errors 8 boxes*). Indeed, error rate was diminishing drastically with age in the control group, but changes with age in the 22q11DS group was minimal. Significant group effects were found in all loads (*Between errors 4 boxes* p<0.001; *Between errors 6 boxes* p<0.001; *Between errors 8 boxes* p<0.001) characterized systematically by higher error rates in the 22q11DS group.

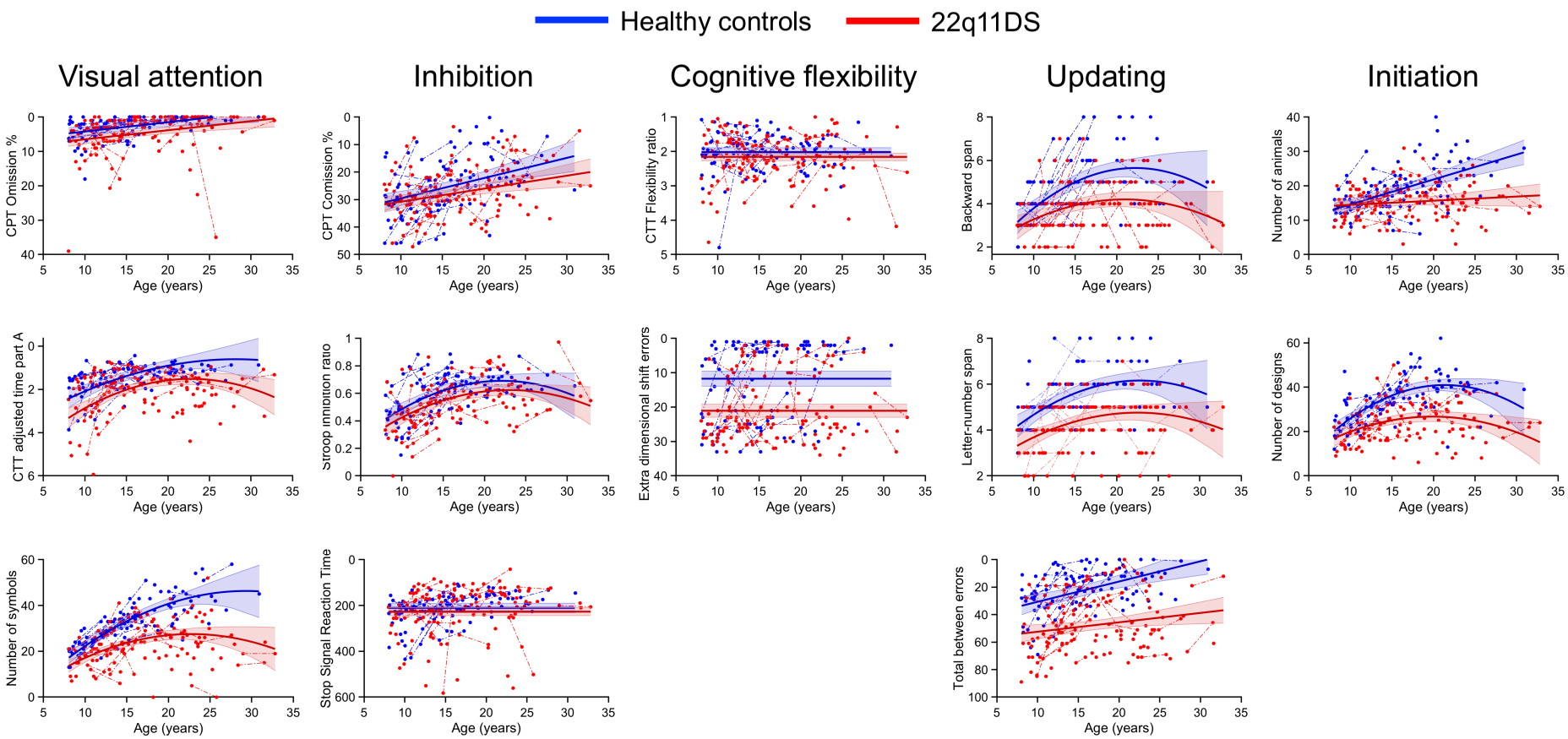

Figure 2 Developmental trajectories of executive functions and attention domains. The solid lines show the developmental model best fitting the data. Data points from a single subject are connected by a dotted line. Scores from the 22q11DS group are displayed in red and healthy controls in blue. Note that in all sub-figure, scores depicted toward the top of the figure represent better performance whereas score depicted toward the bottom represent worse performance. To improve clarity of interpretation, scales of the y axis have therefore been reversed when lower scores indicated better performance (e.g., less errors), with low scores at the top of the figure and high scores at the bottom.

Finally, for initiation, significant group effects with better performance in the control group was found for *Number of animals* ($p<0.001$) and *Number of designs* ($p<0.001$). In both variables, significant interactions with age showed that performance of the 22q11DS group prematurely reached a plateau compared to healthy controls (*Number of animals*: $p<0.001$ and *Number of designs*: $p=0.007$).

Discussion

The goal of this study was to examine, in several domains and with multiple tasks per domain, EF and focal attention, to identify possible atypical developmental patterns in 22q11DS and clarify their neuropsychological profile. Thereby, this study confirms and extends previous results on the developmental trajectories in 22q11DS, by examining a broad age range (8-35 years) partially composed of longitudinal data. Overall, results show that different trajectories emerge depending on the domain or the task examined. Age-related improvement was observed in the large majority of the studied variables. When compared to healthy controls, trajectories of 22q11DS participants showed both developmental deficits and developmental lags.

No evidence for cognitive decline

Results from the 22q11DS group revealed age-related performance increase (in terms of raw score) for almost all examined domains of EF and focal attention. This is in line with the literature on healthy controls demonstrating continuous development during childhood, extending to early adulthood (e.g., Romine & Reynolds, 2005). Overall, examination of raw scores yielded patterns of both developmental deficits (i.e., lower levels of performance but regular improvement) and developmental lags (i.e., improvement at a slower pace with age) in this sample during this age window. However, neither developmental maturation (i.e., initial cognitive impairment but development catches up with the control group) nor deterioration (i.e., decline in absolute ability) were observed. Previous studies examining changes in

neurocognitive measures in samples with smaller age-ranges have often suggested patterns of developmental deficit in 22q11DS (Antshel, Fremont, Ramanathan, & Kates, 2017; Chawner et al., 2017; Hooper et al., 2013). Some exception are observed, with evidence for a developmental maturation of processing speed in Chawner et al. (2017), as well as evidence for a developmental lag of sustained attention in Hooper et al. (2013) and working memory (verbal and visual) in Antshel et al. (2017). Discrepancies with our findings could come either from the limited age window examined in these studies (as they did not considered adults but only focused on development across childhood) or from the study-design (i.e., mix of cross-sectional and longitudinal measures) in our study. Nevertheless, in line with our results, no previous study reported deterioration for measures of EF and focal attention. Indeed, as previously demonstrated, prevalence of individual decline from one visit to another was observed but did not differ from the control group, reflecting rather developmental fluctuation than a 22q11DS-specific pattern of deterioration (Chawner et al., 2017). Regarding cognitive decline, previous studies using overall intellectual abilities as indicator of cognitive functioning have shown that some individuals with 22q11DS do present a more severe deterioration over time (Duijff et al., 2013). Particularly, in a large sample from a collaborative study regrouping over 800 22q11DS carriers, early cognitive decline of verbal intellectual abilities (verbal IQ) was suggested as a robust indicator for developing a psychotic illness (Vorstman et al., 2015). However, results should be interpreted carefully as the analyses was based on standardized composite scores. Indeed, a drop in standardized scores reads as a decline even though it could occur from two different processes: either from a loss of ability (deterioration) or slower pace of improvement leading to a gap compared to controls (lag).

Diversity of developmental patterns across domains

Exploration of multiple cognitive domains in the same sample highlighted different patterns of developmental trajectories across domains. This in line with previous results who found

different developmental models depending on the domains examined (Antshel et al., 2017; Maeder et al., 2016; Shapiro et al., 2014). In Chawner et al. (2017) different patterns across cognitive domains were also reported, however measures of EF and attention (spatial working memory, spatial planning, set-shifting, visual attention) only yielded a single type of pattern. Differences likely come from methodological divergence between studies (task chosen, age sample, cross-sectional or longitudinal design). Overall, the present results and previous literature suggest that EF and focal attention are not affected as a unitary construct in 22q11DS, but that there is a diversity of developmental patterns across domains. Indeed, some show a steady improvement with age (developmental deficit) whereas others display a gap that widens with age (developmental lag).

Only two domains (inhibition and initiation) yielded one consistent developmental pattern on all tasks, while the other three (flexibility, updating and visual attention) yielded different developmental models, depending on the task. Furthermore, using different outcome measures (speed vs. accuracy) showed that accuracy mostly distinguished 22q11DS from controls, whereas speed sometimes did not show any group differences (e.g., for *Stop-Signal Reaction Time*). These results highlight that even when measuring the same domain, tasks, modality of testing (verbal vs. non-verbal) or even outcome measure can yield different developmental pattern. In this context, future studies may use latent variable approaches to model variables sharing variance, to extract communalities and to better understand similar patterns of development in 22q11DS.

Clinical implications

Results from this study have several implications for clinicians and caregivers. First, different patterns of development were observed across domains and sometimes across tasks from one domain or outcome measure. This result should be considered in relation to neuropsychological assessments. Not only does it suggest that different types of indicators can give very different

results, but also that depending on the chosen task or indicator, performance could be only partially represented. With regards to intervention, specific patterns of development for a certain ability should help guiding professionals towards different strategies. Indeed, particular attention should be given to domains exhibiting developmental lag to prevent the gap from widening during adolescence. For example, by introducing early cognitive training targeting the affected domain. Similarly, in domains showing developmental deficits, compensatory strategies could be implemented depending on identified strength in the cognitive profile.

Second, across all domains of EF and focal attention, impairments and/or divergence of developmental trajectories were observed in childhood or early adolescence. This highlights that cognitive and educational interventions should be implemented as early in childhood as possible to prevent or slow down future impairments.

Limitations

Firstly, although the examined age range was much larger in our sample compared to most of the previous studies, it remained limited from school-age to young adulthood. On one hand, we had to limit the age range to ensure that the same task could be used across the entire sample. On the other hand, as the Swiss longitudinal cohort focuses on childhood and adolescence, participants older than 35 years old are only rarely included. Literature on adults 22q11DS carriers older than 30 is still very scarce, however there is evidence for early-onset of neurodegenerative disorders (such as Parkinson's disease), increasing the risk for cognitive decline in this population (Butcher et al., 2013; Fung et al., 2015). Future studies should further extend the age range in order to investigate lifespan developmental trajectories in more detail.

Secondly, only cognitive tasks were selected for this study. Additional questionnaires with observations from the parents could provide supplementary information to the developmental picture of EF and attention in 22q11DS, by increasing ecological validity. For example, analysis of the predicting value of questionnaires measuring EF suggested that parents reports are more

sensitive than cognitive performance when it comes to identify children at risk of negative developmental outcome (Albert et al., 2018).

Finally, patterns of maturation were solely examined based on accuracy or speed indicators extracted from behavioral tasks. Previous studies using functional magnetic resonance imagery (fMRI) to study working memory have shown significant differences in brain activation during a task, while behavioral results were comparable between groups (Harrell et al., 2017; Montojo et al., 2014). According to the evidence of atypical maturation of brain regions who support these abilities in 22q11DS, future work should focus on linking neuroimaging and behavioral results in order to get a more fine-grained understanding of the developmental mechanisms and their underlying neural pathways.

Conclusion

In sum, the current findings confirm and extend knowledge on the developmental patterns of EF and focal attention in 22q11DS. Results highlight age-related improvements on most of the domains examined, although some tasks did not. Compared to previous research, including a larger age range allowed to uncover not only developmental deficits of individuals with 22q11DS (i.e., lower levels of performance), but also developmental lags for certain cognitive domains (i.e., delayed onset or slower pace of developmental improvement). Specifically, individuals with 22q11DS not only had worse inhibition, but our findings show that their initiation skills developed later than those of healthy controls. In contrast, developmental differences between the two groups seem less clear regarding cognitive flexibility, updating and visual focal attention, for which performance seem strongly depend on the task that is selected to assess the domain. Overall, results highlight how EF and focal attention are not affected as a unitary construct, but instead different patterns of development are found across domains and tasks in 22q11DS requiring specific and adapted intervention strategies.

Study 3 - Long-term verbal memory deficit and associated hippocampal alterations in 22q11.2 deletion syndrome[3]

Abstract

Background: 22q11.2 deletion syndrome (22q11DS) is a genetic disease associated with an increased risk for schizophrenia and a specific cognitive profile. In this paper, we challenge the current view of spared verbal memory in 22q11DS by investigating verbal memory consolidation processes over an extended time span to further qualify the neuropsychological profile. Our hypotheses are based on brain anomalies of the medial temporal lobes consistently reported in this syndrome.

Methods: 84 participants (45 with 22q11DS), aged 8-24 years old, completed a verbal episodic memory task to investigate long-term memory on four different time delays. We compared trajectories of forgetting between groups (22q11DS vs. controls) and analyzed performance inside the 22q11DS sample through cluster analyses. Potential links between memory performance and volume of the hippocampal subfields were examined.

Results: We showed accelerated long-term forgetting (ALF) in the 22q11DS group, visible after a delay of one day. Using mixed model, we showed significant differences in the shape of memory trajectories between subgroups of participants with 22q11DS. These sub-groups differed in terms of memory recognition, intellectual functioning, positive psychotic symptoms and grey matter volume of hippocampal subfields but not in terms of age.

Conclusions: By investigating memory processes on longer delays than standardized memory tasks, we identified deficits in long-term memory consolidation leading to ALF in 22q11DS. Nevertheless, we showed that a subgroup of patients had larger memory consolidation deficit

[3] This study is a reprint of the article: Maeder, J., Sandini, C., Zöller, D., Schneider, M., Bostelmann, M., Pouillard, V., Caroni, P., Kliegel, M., & Eliez, S. (2020). Long-term verbal memory deficit and associated hippocampal alterations in 22q11.2 deletion syndrome. *Child Neuropsychology*, 26(3), 289–311. Retrieved from https://doi.org/10.1080/09297049.2019.1657392

associated with lower intellectual functioning, higher rates of positive psychotic symptoms and hippocampal alterations.

1. Introduction

Chromosome 22q11.2 deletion syndrome (22q11DS) is a genetic disorder associated with an increased risk for psychopathology and a specific cognitive profile (Henry et al., 2002; Schneider, Debbané, et al., 2014). Indeed, the presence of this microdeletion is recognized as one of the highest risk factors for the development of psychosis or schizophrenia spectrum disorder (Schneider, Debbané, et al., 2014).

Brain development abnormalities have been reported from a structural and functional perspective in this population (Gothelf, Schaer, & Eliez, 2008; Padula, Schaer, Scariati, Maeder, et al., 2017; Scariati et al., 2016). More specifically, alterations of the medial temporal lobe, with a reduction of the body of the hippocampus have been consistently observed (Debbané et al., 2006; DeBoer et al., 2007; Eliez et al., 2001; Kates et al., 2006). Furthermore, in a mouse model of the human 22q11.2 microdeletion, alterations in the neuronal physiology of the hippocampus have been shown, suggesting decreased interneuron activity and deficits in long-term potentiation (Drew et al., 2011). As medial temporal lobes play a key role in memory functions, alterations have an impact on memory performance (Squire, Stark, & Clark, 2004).

On a behavioral level, a dissociation between verbal and visual memory processes has been described in 22q11DS. Indeed, probably due to poorer visuospatial and visuo-attentional processes, visual memory acquisition is not optimal and visual memory is generally reported as impaired (Bostelmann et al., 2017; Lajiness-O'Neill et al., 2005; Woodin et al., 2001). By contrast, it has been argued so far that verbal memory stands out as a relative strength in the 22q11DS cognitive profile (Jacobson et al., 2010; Lajiness-O'Neill et al., 2005; Lewandowski et al., 2007). However, while memory consolidation is known to occur over long delays such

as weeks, months or even years (Squire & Alvarez, 1995), to our knowledge, no study has examined verbal memory performance on delays beyond thirty minutes in the 22q11DS population. Therefore, although verbal learning performance seems relatively preserved, it is unknown whether long-term consolidation of memory is affected in 22q11DS. Interestingly, reports from individuals affected by 22q11DS and their families point to forgetfulness and memory loss over time, which challenges the general assumption of spared verbal long-term memory. We argue that longer recall delays need to be investigated in order to fully grasp verbal memory performance and consolidation processes in 22q11DS.

Memory consolidation can be defined as the neurobiological process of strengthening and stabilizing memories, which initially exist in an easily disrupted state (Bisaz, Travaglia, & Alberini, 2014). Once a memory has been consolidated, its reactivation through recall will revert the trace to a labile state. Another iteration of consolidation processes, known as reconsolidation, subsequently occurs in order to bring the memory trace back to a stable state (Alberini & Ledoux, 2013). When measuring forgetting, failure of consolidation or reconsolidation processes are assumed to lead to an accelerated long-term forgetting (ALF). ALF refers to the abnormally rapid pace at which memory fades, even though memories are encoded and retained normally over delays of thirty minutes (Elliott, Isaac, & Muhlert, 2014). Given that standardized tasks commonly used to assess episodic memory involve delays that do not exceed thirty minutes, an ALF phenomenon could go undetected using available tools.

On a behavioral level, memory consolidation can only be measured indirectly through retrieval. As retrieval can fail due to defects in accessing the memory (even if the memory is correctly stored), memory recognition paradigms are generally used as a complementary measure. It has been shown that memory recognition is based on two components: recollection and familiarity (Mandler, 1980; Squire et al., 2004). The latter is quickly accessible, contains no information about the context and depends on more adjacent cortex, whereas the former provides context

of encounter and depends mainly on the hippocampus (Eichenbaum, Yonelinas, & Ranganath, 2007; Squire et al., 2004).

Studying the characteristics of memory consolidation in 22q11DS is not only relevant for the understanding of the neuropsychological profile of the syndrome but may also provide important insights regarding preclinical stages of psychosis. Indeed, cognitive impairments, including episodic memory deficits, are reported as one of the core features of psychosis and schizophrenia spectrum disorders (Antoniades et al., 2017; Jahshan, Heaton, Golshan, & Cadenhead, 2010). Signs of memory deficits have also been reported in prodromal stages of schizophrenia as well as first-episode patients, and seem to be stable throughout the stages of the disease (Bora & Murray, 2014). Episodic memory deficits could therefore be considered as an endophenotype or an intermediate phenotype in the development of psychosis (Cannon, 2005; Owens et al., 2011). In line with this, studying episodic memory consolidation in a population at high risk for schizophrenia such as 22q11DS could help understand factors of interest in the emergence of psychosis.

Finally, despite a similar genetic etiological origin, relatively high levels of heterogeneity can be observed amongst individuals with 22q11DS in terms of their phenotypical expression (Philip & Bassett, 2011; Swillen & McDonald-McGinn, 2015). Therefore, when aiming at a fine-grained understanding of the syndrome, but also when seeking accurate predictors of later outcome, it becomes relevant to move beyond group comparisons (patients against controls). In line with this, several studies have attempted to identify subgroups of patients based on different variables (e.g., Sinderberry et al., 2013; Weinberger et al., 2016). However, the characterization of subgroups based on long-term memory consolidation has not yet been performed in 22q11DS.

1.1. Aims and hypothesis

In the present study, we first aimed to investigate long-term memory processes in 22q11DS and controls. Due to the deficit reported in visuo-attentional processes, possibly influencing the encoding of visual information, we focused on the verbal modality for which encoding seems to be relatively preserved (Debbané et al., 2008). As previous studies showed preserved verbal memory performance using standardized tools after a delay of thirty minutes, we extended the recall delays to one day, one week and one month. Our first hypothesis was that verbal memory recall would be similar to controls after a delay of thirty minutes but lower on longer delays, which would represent indicators of an ALF phenomenon in this population. Additionally, since retrieval processes involved in free recall can sometimes be deficient, we also explored recognition memory as a complementary measure of memory consolidation. We predicted that if consolidation processes were altered, trajectories of recognition through time would follow the same path. Indeed, familiarity processes would not help recognition performance and a decline will also appear after a delay of time.

Our second aim was to determine whether subgroups of patients could be identified based on their long-term verbal memory profile. We hypothesized that alterations in the trajectory of memory retention would not be ubiquitous to 22q11DS but could selectively affect a sub-group of patients. Furthermore, in line with findings reporting an association between verbal memory impairments and psychosis (Owens et al., 2011), we hypothesized that individuals with poorer memory consolidation performance would display higher rates of psychotic symptoms.

Finally, the third aim was to investigate neural correlates of the behavioral findings. We hypothesized more important rates of volumetric reductions of the medial temporal lobe, in individuals with poorer performance on the memory task.

2. Method

2.1. Participants

Eighty-four participants (of which 45 with 22q11DS) completed an extensive series of assessments including cognitive functioning, clinical symptomatology and brain imaging as part of an ongoing longitudinal study on 22q11DS (Geneva cohort) (e.g., Schaer et al., 2009; Schneider, Van der Linden, et al., 2014). Participants were recruited through advertisement in patient association newsletters and word-of-mouth. The presence of a 22q11.2 deletion was confirmed using quantitative fluorescent polymerase chain reaction (QF-PCR). The control group consisted of siblings from participants affected with 22q11DS (84%) and community controls. Participants with 22q11DS and controls were aged between 8 and 24 years and did not differ in terms of age or gender (see Table 1). Written informed consent, based on protocols approved by the Swiss Ethical Committee of Geneva (CCER, Switzerland), was obtained for all participants and their parents (if the participant was younger than 18 years old).

Table 1 Participant characteristics, psychiatric diagnosis and psychotropic medication

			Diagnostic group		Comparison		
			22q11DS	Controls	ANOVA	Pearson's Chi-square	p-value
N			45	39			
Gender (male (%))			20 (44.444%)	16 (41.025%)		0.1	0.082
Age (mean (SD))			16.050 (4.942)	14.166 (5.039)	2.981		0.088
Full Scale IQ (mean (SD))			71.444 (13.560)	114.487 (15.231)	187.736		**<0.001**
Psychiatric diagnosis (N (%))		Simple phobia	13(28.888%)				
		Attention deficit disorder	14 (31.111%)				
		Generalized anxiety	9 (20%)				
		Major depressive episode	2 (4.444%)				
		Psychosis	4 (8.888%)				
		Obsessive-compulsive disorder	1 (2.222%)				
Psychotropic medication (N(%))	Total		17 (37.777%)				
	Categories	Methylphenidate	11 (24.444%)				
		Antidepressants	8 (17.777%)				
		Antipsychotics	9 (20%)				
		Antiepileptic	0 (0%)				
		Anxiolytics	1 (2.222%)				

Significant values at the 0.05 level are displayed in **bold**

2.2. Material

2.2.1. Long-term memory task

To assess verbal episodic memory, we created a word-learning task, inspired by the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1958). Task design and different steps is

summarized in supplementary materials, Figure S1. We used the four wordlists of the RAVLT (A, B, C & D) as targets. Created to be of equal difficulty, these lists consisted in frequent words from the French language (see Supplementary material, Table S1). Learning phase: words were read out loud by the examiner at a regular rhythm of 1 per 3 seconds. To limit the influence of working memory on outcome, a short filler task was performed at the end of each presentation, before proceeding with the recall. The filler task consisted in backwards counting (e.g., 100-1; 200-2; 300-6) during 30 seconds. To avoid recency or primacy effects, stimuli were read in a randomized order, different at each trial. The complete list of 15 words was read at each presentation. After the filler task, participants were instructed to freely recall as many words as they could remember, even those already recalled in a previous learning trial, in the order they chose. Productions were classified as correct (target word) or incorrect (non-target word or repetition of a word already said), no feedback was provided. To avoid over-learning or discouragement to the task, an 80%-success criterion (12 words) or a maximum of 6 trials was established, at which point the learning phase was over. Variables of interest for this phase were: number of presentations of the words to reach the criterion (trial to reach criterion) and maximum of correct words recalled at any stages of the learning phase (word max learned). Recall and recognition phase: participants were asked to freely recall the words after four different time delays (thirty minutes, one day, one week and one month). Again, productions were classified as correct (target word) or incorrect (non-target word or repetition of a word already said). After each free recall without feedback, participants were asked to recognize the 15 target words mixed with 15 distractors (see supplementary material, Table S2). The distractors consisted in words that were semantically or phonetically similar to the targets (see Supplementary material, Table S3) and were different for each delay (thirty minutes, one day, one week, one month) to avoid a familiarity effect from delay to delay. Variables of interest for this phase were: number of words freely recalled at each delay (free recalls at thirty minutes,

one day, one week and one month) and number of words correctly recognized as target or distractor (recognition at thirty minutes, one day, one week and one month).

To really grasp the consolidation of memory over long periods of time, this study design extends over a month and beyond experimental conditions provided by laboratory testing. Indeed, only the first steps of the task (learning phase and thirty minutes recall) were conducted in laboratory setting. Recalls and recognitions after delays of one day, one week and one month were conducted remotely, via Skype© (Microsoft). We attempted to control for most external factors with the following measures: (1) the long-term memory task was done with the same examiner from the first to the last step; (2) stimuli were stored in a box and a reference to the box was made every time the words were recalled (e.g., "*Do you remember this box, what was in it. Can you remember the words I read to you that were stored in this box*"); (3) for recalls at delays of one day, one week and one month, an appointment was set with the participants on Skype but no specific information on what was going to happen was shared with the participant; (4) during Skype appointments, several misleading tasks (answering general knowledge questions, visual reasoning matrix completion) were done with the participant before or after the recall and recognition task so that the program of the next appointment could not be expected; (5) at the end of the last step (one month delay), we asked the participants (a) if they expected the purpose of the Skype appointments, and (b) if they had used a specific strategy to learn or remember the words they were presented with.

2.2.2. Measure of intelligence

All participants completed a Wechsler scale of intelligence to assess reasoning abilities. Children and adolescents up to 16 years old completed the Wechsler Intelligence Scale for Children (WISC-III or IV; Wechsler, 1991, 2004). Participants from 17 years and up completed the Wechsler Adult Intelligence Scale (WAIS-III or IV; Wechsler, 1997a, 2011).

2.2.3. Clinical assessment: All participants with 22q11DS and their caregivers were interviewed by a trained psychiatrist using the computerized Diagnostic Interview for Children and Adolescents-Revised (DICA-R; Reich, 2000) or the Structured Clinical Interview for DSM-IV Axis I (SCID-I; First et al., 1996). The psychotic disorders supplement of the Schedule for Affective Disorders and Schizophrenia for School-Age Children Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) was also administered to all participants. Psychotic symptoms were assessed using the Structured Interview for Prodromal Syndromes (SIPS; Miller et al., 2004), as well as the Positive And Negative Syndrome Scale (PANSS; Kay et al., 1967) and the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962). Positive and negative dimension were compared individually, for the SIPS, we also examined the disorganized dimension; and for the PANSS we compared the negative symptoms through the amotivation dimension and the expressive dimension based on previous work from our lab (Schneider, Van der Linden, et al., 2014). Information about the presence of psychiatric diagnoses and use of psychotropic medication at the time of testing is summarized in Table 1.

2.2.4. Neuroimaging

Neuroimaging was available in 35/45 patients who underwent verbal memory assessment. T1-weighted structural MRI images were acquired using a three-dimensional volumetric pulse sequence with Siemens Trio 3T scanners (sequence parameters: TR=2500ms, TE=3ms, flip-angle=8°, acquisition matrix=256×256, field of view=22cm, slice thickness=1.1mm, and 192 slices). Images were imported in FreeSurfer software package version 6.0 (https://surfer.nmr.mgh.harvard.edu/) for an automated segmentation of hippocampal subfields and total hippocampal volume (Iglesias et al., 2015). The approach makes use of an atlas constructed from high very high resolution ex-vivo images with Bayesian inference to segment the hippocampus in 12 subfields: Parasubiculum, Presubiculum, Subiculum, CA1, CA2/3, CA4, Granulate Cells of the Molecular Layer of the Dentate Gyrus (GC-ML-DG), Molecular

Layer, Hippocampal Fissure, Fimbria, Hippocampal Tail, and Hippocampus-Amygdala Transition Area (HATA) (Iglesias et al., 2015). The quality of the segmentation was checked as explained in (Mancini et al., 2019). Measures of supra-tentorial brain volume were also extracted using FreeSurfer.

2.3. Statistical analyses

2.3.1. Memory performance and memory retention trajectory

Learning performance variables (assessed by "trial to reach criterion" and "word max learned") were not normally distributed (respectively, for 22q11DS: $D(45) = 0.244$, $p < 0.001$; $D(45) = 0.235$, $p < 0.001$; for Controls: $D(39) = 0.203$, $p < 0.001$; $D(39) = 0.304$, $p < 0.001$;) therefore compared between groups using non-parametric tests (Mann-Whitney test). Trajectories of memory retention and recognition over time were examined using mixed model regression analyses in MATLAB R2014 (MathWorks), as described in previous studies (Martina Franchini et al., 2018; Mancini et al., 2019; Mutlu et al., 2013). These analyses allowed us to identify shape differences (i.e., curves that do not follow the same path) or intercept differences (i.e., curves that follow a parallel path but not on the same intercept) between two groups (22q11DS vs. controls or subgroups within 22q11DS). In complementary analyses, IQ, age, and IQ + age were used as covariates. Groups were then compared on a series of variables (age, intellectual functioning, positive and negative psychotic symptomatology) using non-parametric tests (Mann-Whitney test and Wilcoxon signed rank test). The influence of age on general memory performance was examined using Spearman correlations. The Benjamini-Hochberg (Thissen et al., 2002) multiple comparison correction was applied to all statistical analyses. For non-parametric tests, effect sizes were calculated using eta square formula. For the mixed model, the p-values are derived with a likelihood ratio test comparing the full models (including group-by-intercept effect respectively a group-by-shape effect) to the reduced

models (without the respective group effects). Details on the fitted models as well as likelihood ratios are summarized in Table 2.

Table 2: Differences in trajectories of memory retention and recognition between groups of 22q11DS and Control

			Group effect		Slope	
	22q11DS intercept, beta1, beta2 (SD)	Controls intercept, beta1, beta2 (SD)	Likelihood ratio (df)	Group effect (*p*-value)	Likelihood ratio (df)	*p*-value
Memory retention (raw score)	12.394(+/-0.260), -2.163(+/-0.247), 0.186(+/-0.056)	12.586(+/-0.279), -1.477(+/-0.266), 0.152(+/-0.060)	14.933(3)	0.002	11.350(2)	0.003
Memory retention (raw score) covariate with IQ	13.491(+/-0.308), -2.163(+/-0.248), 0.186(+/-0.056)	11.320(+/-0.341), -1.477(+/-0.266), 0.152(+/-0.060)	22.184(3)	<0.001	12.197(2)	0.002
Memory retention (raw score) covariate with age	12.3351(+/-0.259), -2.163(+/-0.247), 0.186(+/-0.056)	12.636(+/-0.278), -1.477(+/-0.266), 0.152(+/-0.060)	15.940(3)	0.001	11.293(2)	0.004
Memory retention (raw score) covariate with age and IQ	13.441(+/-0.306), -2.163(+/-0.247), 0.186(+/-0.056)	11.378(+/-0.339), -1.477(+/-0.266), 0.152(+/-0.060)	21.093(3)	<0.001	12.136(2)	0.002
Recognition (raw score)	29.161(+/-0.399), 0.552(+/-0.368), -0.239(+/-0.072)	30.006(+/-0.429), -0.140(+/-0.396), -0.032(+/-0.077)	13.334(3)	0.004	11.168(2)	0.004
Recognition (raw score) covariate with IQ	30.591(+/-0.223), -0.642(+/-0.084)	29.895(+/-0.246), -0.300(+/-0.091)	7.723(3)	0.021	7.492(2)	0.006
Recognition (raw score) covariate with age	29.151(+/-0.340), 0.552(+/-0.368)	30.019(+/-0.428), -0.140(+/-0.394)	13.580(3)	0.004	11.168(2)	0.004
Recognition (raw score) covariate with age and IQ	29.3728(+/-0.423), 0.552(+/-0.370)	29.7622(+/-0.457), -0.140(+/-0.398)	11.504(3)	0.009	11.359(2)	0.003

beta1 = linear time effect of trajectory
beta2 = quadratic time effect of trajectory
SD = Standard Deviation

2.3.2. Clustering of Patients According to Trajectories of Memory Retention:

The k-means clustering method was used to split the patients' sample into two subgroups based on their memory retention performances. Recall scores at each time delay were defined as the grouping variables. The algorithm groups together subjects with a similar variable of interest throughout multiple observations by minimizing the distance between each observation point and the mean of the class (Twisk & Hoekstra, 2012). In this context the algorithm yielded groups of individuals with similar memory retention performance across multiple assessments, indicating similar longitudinal trajectories of memory retention over time. We specifically employed K-means clustering as implemented in Matlab, with 10000 iterations, yielding subgroups of subjects with similar trajectories of memory retention. We subsequently employed linear mixed model regression (Mutlu et al., 2013) to compare subgroups of patients to each other and to healthy controls according to trajectories of memory retention and recognition. In

the mixed model analyses, we added a complementary analysis with age as a covariate for memory retention and recognition. Subgroups of patients were furthermore compared to each other according to clinical and neuropsychological variables of interest as well according to measures of hippocampal morphology. Again, the Benjamini-Hochberg multiple comparison correction was applied to all statistical analyses. Effect sizes are displayed on Table 5 and details on the fitted models as well as likelihood ratios are summarized in Table 4.

2.3.3. Neuroimaging

Grey matter volume of hippocampal subfields as well as of the whole hippocampus were compared between clusters of patients divided according to their trajectory of memory retention. Statistical differences were evaluated non-parametrically using Wilcoxon rank sum test after accounting for the effect of age, gender, supra-tentorial brain volume and performance IQ with linear regression. Effect sizes were computed using Hedges' g.

3. Results

3.1. Group comparison (22q11DS vs. typically developing controls)

3.1.1. Learning

Mann-Whitney tests indicated that there was no significant difference in the amount of trials needed to reach the learning criterion between groups ($Mdn_{22q11DS} = 3$, $Mdn_{Ctrl} = 3$, $U = 718.500$, $z = -1.470$, $p = 0.142$, $\eta^2 = 0.026$), nor in the maximum amount of words recalled at the end of the learning phase ($Mdn_{22q11DS} = 12$, $Mdn_{Ctrl} = 12$, $U = 729.500$, $z = -1.416$, $p = 0.157$, $\eta^2 = 0.024$). Therefore, learning performance is comparable between the two groups.

3.1.2. Recall

we compared trajectories of free recall performance throughout each time delay (thirty minutes, one day, one week and one month) in 22q11DS and controls using mixed model regression (Figure 1A). We observed a significant difference in the shape of the trajectories with time (p

= 0.002; see Table 2 for details). When full-scale IQ was entered as a covariate in the analyses, the difference in shape remained significant ($p < 0.001$), characterized by a steeper forgetting slope in the 22q11DS group with time. The same observation was made for age in covariate ($p = 0.001$) and combined age and full-scale IQ ($p < 0.001$). With Mann-Whitney tests we showed that both groups had similar recall performance after thirty minutes ($Mdn_{22q11DS} = 11$, $Mdn_{Ctrl} = 11$, $U = 874.500$, $z = -0.027$, $p = 0.978$, $\eta^2 < 0.001$), After Benjamini-Hochberg correction (new threshold for statistical significance $p < 0.013$), the control group had significantly higher scores than the 22q11DS group after one day ($Mdn_{22q11DS} = 9$, $Mdn_{Ctrl} = 10$, $U = 511.000$, $z = -3.316$, $p = 0.001$, $\eta^2 = 0.132$) and one month ($Mdn_{22q11DS} = 7$, $Mdn_{Ctrl} = 10$, $U = 506.500$, $z = -3.345$, $p = 0.001$, $\eta^2 = 0.135$). The difference between group at one week was significant ($Mdn_{22q11DS} = 8$, $Mdn_{Ctrl} = 9$, $U = 609.000$, $z = -2.427$, $p = 0.015$, $\eta^2 = 0.071$), but did not survive multiple comparison. Analyzing the dynamic of memory loss through post-hoc comparisons confirmed the presence of different trajectories between groups. In the control group, using Wilcoxon signed rank tests, after Benjamini-Hochberg correction (new threshold for statistical significance $p < 0.025$), a significant drop in performance was observed between one day and one week ($Mdn_{one\_day} = 10$, $Mdn_{one\_week} = 9$, $Z = -3.788$, $p < 0.001$, $\eta^2 = 0.378$), whereas comparisons between thirty minutes and one day or one week and one month did not differ ($p > 0.778$). As for the 22q11DS group, performance dropped significantly between each time delay ($Mdn_{thirty\_min} = 11$, $Mdn_{one\_day} = 9$, $Z = -4.308$, $p < 0.001$, $\eta^2 = 0.422$; $Mdn_{one\_day} = 9$, $Mdn_{one\_week} = 8$, $Z = -4.066$, $p < 0.001$, $\eta^2 = 0.376$) and tended to stabilize between one week and one month ($Mdn_{one\_week} = 8$, $Mdn_{one\_month} = 7$, $Z = -1.966$, $p = 0.049$, $\eta^2 = 0.088$) since the comparison did not survive multiple comparison correction (new threshold for statistical significance $p < 0.008$).

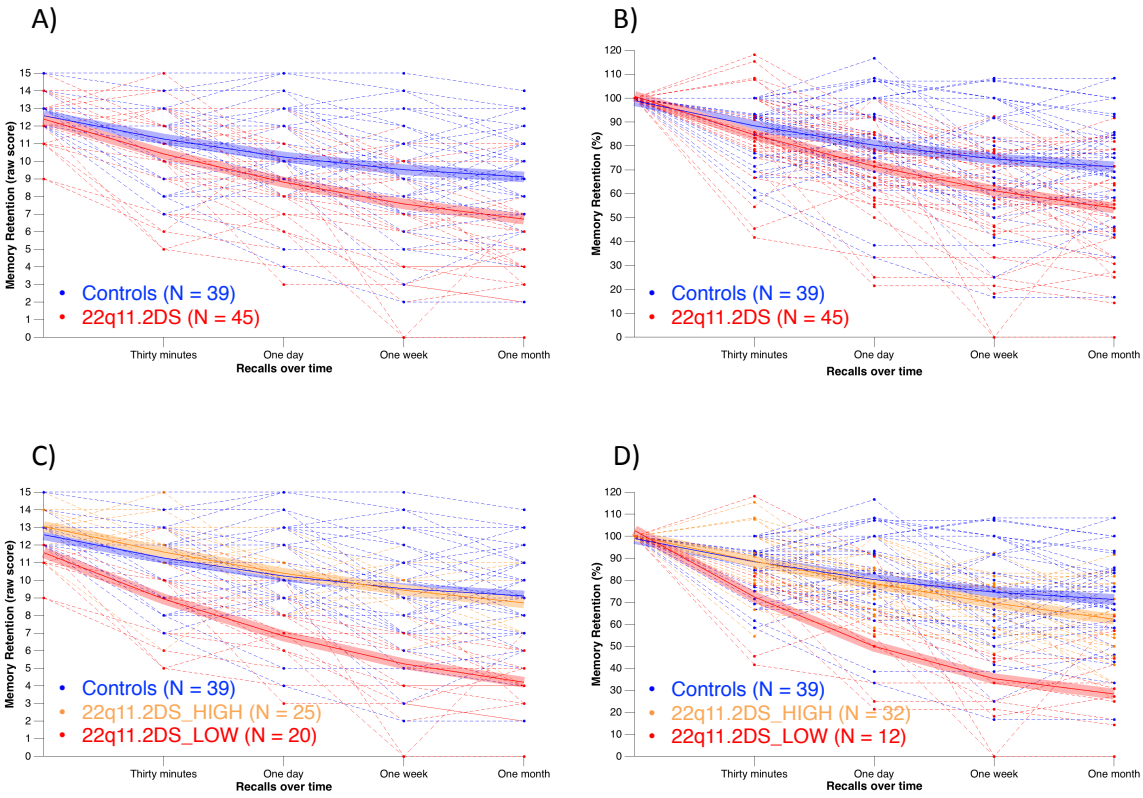

Figure 1: Group comparison of long-term memory trajectories through time

3.1.3. Recognition

we compared both groups on correct recognition performance, using the amount of words correctly identified as target or distractor (total of 30). There was a significant difference in shape of the trajectories with time ($p = 0.004$) (Figure 2A; see Table 2 for details). Results were similar after adding full-scale IQ ($p = 0.021$), age ($p = 0.004$) as well as full-scale IQ combined ($p = 0.009$) as covariates. A Mann-Witney test indicated that, after multiple comparison correction (new threshold for statistical significance $p < 0.018$) there was poorer recognition performance in the 22q11DS group at thirty minutes ($Mdn_{22q11DS} = 30$, $Mdn_{Ctrl} = 30$, $U = 664.500$, $z = -2.483$, $p = 0.013$, $\eta^2 = 0.074$) and one month delay ($Mdn_{22q11DS} = 28$, $Mdn_{Ctrl} = 30$, $U = 508$, $p = 0.001$, $\eta^2 = 0.141$).

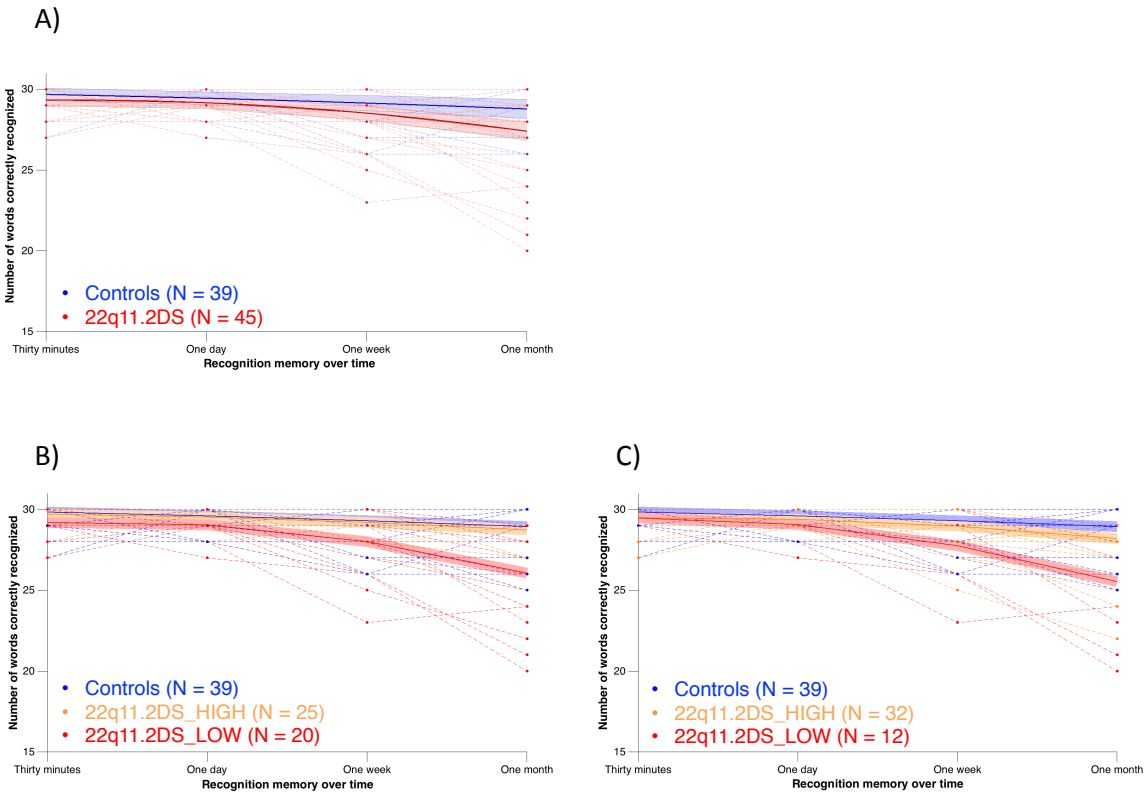

Figure 2: Group comparison of recognition memory trajectories through time

3.1.4. Strategy analysis

during the learning phase, only 7 individuals (7.9%) reported the use of a specific strategy to learn the words. From this sample 5 (1 individual with 22q11DS) tried to do semantic associations and 2 (none with 22q11DS) used mental imaging to remember the words. For memorization, on the whole sample, approximatively half of the participants (48.9%) reported they knew they would have to repeat the words later on. There was no difference between 22q11DS and control participants on this matter (χ^2 [1, 88] = 0.164, p = 0.686). Even with half of the sample anticipating the purpose of the task, only 12 participants (13.6%) told us they tried to remember the words in between recalls, mostly just a few minutes before the skype meeting. Both groups did not differ on this with 6 participants in each diagnostic group (χ^2 [1, 88] = 0.182, p = 0.670). No participant reported writing down the words to remember them.

3.2. Correlation with age

As memory performance is reported to increase with age, we investigated the link between age, learning and memory performance in individuals with 22q11DS and typically developing controls using a Spearman one-tailed correlation. Interestingly, almost all the variables reflecting learning and free recall performance in the control group were significantly associated with age (see Table 3). In the 22q11DS group however, only the number of trials needed to reach criterion was significantly associated with age ($r = -2.92$; $p = 0.026$). Recognition performance at any delay was not related to age in either of the two groups.

Table 3 Correlation of memory performance with age

	22q11DS		Controls	
	Age		Age	
	Spearman Correlation	*Sig (1-tailed)*	*Spearman Correlation*	*Sig (1-tailed)*
Number of learning trials	-.292**	0.026	-.453**	0.002
Maximum number of words recalled in learning phase	-0.168	0.134	.320**	0.024
Free recall thirty minutes delay	-0.103	0.251	.449**	0.002
Recognition thirty minutes delay	0.054	0.361	0.116	0.242
Free recall one day delay	-0.005	0.488	.433**	0.003
Recognition one day delay	0.01	0.473	-0.027	0.435
Free recall one week delay	-0.13	0.197	0.219	0.09
Recognition one week delay	-0.14	0.179	-0.112	0.249
Free recall one month delay	-0.097	0.263	.291*	0.036
Recognition one month delay	-0.088	0.283	-0.071	0.335

*** Correlation is significant after Benjamini-Hochberg correction at the 0.027 level (1-tailed)*
** Correlation is significant at the 0.05 level (1-tailed)*

3.3. Cluster analyses

3.3.1. Clustering with raw scores of memory

To account for the heterogeneity of performance in the 22q11DS sample, we performed a cluster analysis to discriminate more homogeneous subgroups of individuals based on raw recall performance. The sample was split in two subgroups, one of 25 individuals having higher global memory performance (22q11DS_HIGH) and another of 20 individuals having lower memory performance (22q11DS_LOW). When comparing their trajectories of memory recalls though time, we found a significant difference in shape ($p < 0.001$) between the two clusters (Figure 1C; see Table 4 for details). Furthermore, both groups differed on learning performance, with a significantly higher number of words recalled at the end of the learning phase ($p < 0.001$,

$\eta^2 = 0.328$) for the 22q11DS_HIGH group, but a comparable number of trials to reach the learning criterion ($p = 0.119$, $\eta^2 = 0.055$; see Table 5). Finally, the 22q11DS_HIGH group exhibited no difference in shape or intercept of memory performance with the control group, whereas the 22q11DS_LOW group had a significant difference in shape of memory performance with the control group ($p < 0.001$). Post-hoc non-parametric group-comparisons showed that participants from the two clusters were comparable in age ($p = 0.798$, $\eta^2 = 0.001$), but differed on intellectual functioning ($F [1,44] = 14.844$, $p < 0.001$, $\eta^2 = 0.257$) and one measure of positive psychotic symptoms (the other ones did not survive the Benjamini-Hochberg correction with a significant threshold at 0.026, see Table 5). No difference was seen with negative psychotic symptoms. The group with lower long-term memory performance had significantly lower IQ and increased positive symptoms. In regard to recognition memory, we compared both clusters on trajectories over time using mixed model. We found a significant difference in shape ($p < 0.001$; see Table 4 for details) between the two clusters (Figure 2B).

Table 4: Differences in trajectories of memory retention and recognition between clustered groups of 22q11DS HIGH and LOW

	Raw clustering		Group effect		Slope	
	22q11DS_HIGH intercept, beta1, beta2 (SD)	22q11DS_LOW intercept, beta1, beta2 (SD)	Likelihood ratio (df)	Group effect (*p*-value)	Likelihood ratio (df)	*p*-value
Memory retention (raw score)	13.054(+/-0.302), -1.575 (+/-0.334), 0.123(+/-0.079)	14.539(+/-0.692), -0.254(+/-0.764), 0.019(+/-0.181)	63.311(3)	<0.001	20.883(2)	<0.001
Memory retention (raw score) covariate with age	12.3351(+/-0.259), -2.163 (+/-0.247), 0.186(+/-0.056)	12.636(+/-0.278), -1.477(+/-0.266), 0.152(+/-0.060)	64.305(3)	<0.001	21.214(2)	<0.001
Recognition (raw score)	29.750(+/-0.645), 0.026(+/-0.593)	31.075(+/-1.479), -1.158(+/-1.358)	21.947(3)	<0.001	18.417(2)	<0.001
Recognition (raw score) covariate with age	29.751(+/-0.645), 0.026(+/-0.592)	31.078(+/-1.477), -1.158(+/-1.357)	21.893(3)	<0.001	18.409(2)	<0.001
	Normalized Clustering		Group effect		Slope	
	22q11DS_HIGH intercept, beta1, beta2 (SD)	22q11DS_LOW intercept, beta1, beta2 (SD)	Likelihood ratio (df)	Group effect (*p*-value)	Likelihood ratio (df)	*p*-value
Memory retention (raw score)	100.174(+/-1.861), -12.281(+/-2.250), 0.705(+/-0.528)	97.747(+/-4.955), 9.506(+/-5.992), -2.467(+/-0.528)	55.617(3)	<0.001	37.607(2)	<0.001
Memory retention (raw score) covariate with age	100.129(+/-1.863), -12.281(+/-2.250), 0.705(+/-0.528)	97.518(+/-4.972), 9.506(+/-5.991), -2.467(+/-1.407)	55.209(3)	<0.001	37.722(2)	<0.001
Recognition (raw score)	30.074(+/-0.251), -0.426(+/-0.112)	28.920(+/+0.669), 0.456(+/-0.298)	14.915(2)	<0.001	14.478(1)	<0.001
Recognition (raw score) covariate with age	30.077(+/-0.251), -0.426(+/-0.112)	28.939(+/-0.671), 0.456(+/-0.298)	14.931(2)	<0.001	14.462(1)	<0.001

beta1 = linear time effect of trajectory
beta2 = quadratic time effect of trajectory
SD = Standard Deviation

Specifically, there was a significant difference in shape between the cluster with low global memory performance (22q11DS_LOW) and the control group ($p < 0.001$), whereas the cluster with high global memory performance (22q11DS_HIGH) did not differ from the control group in shape or intercept.

3.3.2. Clustering with normalized scores of memory (retention percentage)

To exclude influence of learning, we performed a second cluster analysis in the 22q11DS sample using normalized scores that reflect a purer measure of memory retention. To obtain these normalized scores, we divided the raw performance at each time delay by the maximum number of words recalled at the end of the learning phase. We calculated a long-term memory retention percentage score that we used in the clustering. Using this variable, 33 individuals were included in the groups with higher performance (22q11.2D_HIGH) and only 12 had lower performance (22q11DS_LOW). Overall, there was a 76% of overlap with the previous analysis. With this new clustering, we observed a significant difference in the shape of the group's trajectories with time ($p < 0.001$; see Table 4 for details and Figure 1D). Post-hoc non-parametrical analyses showed that while both groups did not differ in terms of age ($p = 0.357$, $\eta^2 = 0.020$) or learning competence ($p > 0.094$, $\eta^2 < 0.069$), the 22q11DS_LOW group had lower intellectual functioning ($F [1,44] = 5.58$, $p = 0.023$, $\eta^2 = 0.114$) but no other difference in psychotic symptoms (see Table 5). Finally, when compared on recognition memory, results were similar to the previous clustering technique: there was a significant difference in shape ($p < 0.001$; see Table 4 for details) between the two clusters (Figure 2C) showing a larger decline in the 22q11DS_LOW cluster. The 22q11DS_HIGH cluster was not different in shape or intercept from the control group, whereas the 22q11DS_LOW cluster had a significantly different shape of trajectory ($p < 0.001$).

Table 5 Clustering in the 22q11DS group

	Raw clustering		Comparison				
	22q11DS_HIGH	22q11DS_LOW	Pearson's Chi-square	ANOVA	Mann-Witney	P-value	Effect size η^2
N	25	20					
Gender (male(%))	10(40%)	10 (50%)	0.45			0.502	
Age (mean (SD))	15.878 (4.768)	16.265 (5.269)		0.067		0.798	0.001
Full Scale IQ (mean(SD))	77.52 (12.689)	63.85(10.638)		14.844		**<0.001**	**0.257**
Number of learning trials (mean(SD))	3.480(1.294)	4.250(1.618)			184	0.119	0.055
Maximum number of words recalled in learning phase (mean(SD))	12.920(0.953)	11.400(1.313)			86.5	**<0.001**	**0.328**
BPRS positive symptoms (mean (SD))	1.733(0.659)	2.633(1.34599)			135	**0.007**	**0.163**
BPRS negative symptoms (mean (SD))	2.306(0.552)	2.350(1.017)			213.5	0.390	0.017
PANSS positive symptoms (mean (SD))	1.405(0.464)	1.914(0.932)			158	0.034	0.102
PANSS negative expressive (mean (SD))	2.456(0.736)	2.630(0.956)			230.5	0.655	0.005
PANSS negative amotivation (mean (SD))	2.820(0.945)	3.075(1.206)			221.5	0.506	0.010
SIPS disorganisation (mean (SD))	0.479(0.403)	1.166(1.224)			140.5	0.047	0.090
SIPS positive (mean (SD))	0.675(0.645)	1.333(1.321)			151	0.096	0.063
SIPS negative (mean (SD))	2.125(0.818)	2.379(0.957)			185.5	0.437	0.014
	Normalized clustering		Comparison				
	22q11DS_HIGH	22q11DS_LOW	Pearson's Chi-square	ANOVA	Mann-Witney	P-value	Effect size η^2
N	34	11					
Gender (male(%))	13 (28.235%)	7 (63.636%)	2.127			0.131	
Age (mean (SD))	15.660(4.579)	17.257(6.013)		0.866		0.357	0.020
Full Scale IQ (mean(SD))	74.029(12.929)	63.455(12.824)		5.58		**0.023**	**0.114**
Number of learning trials (mean(SD))	3.559(1.307)	4.636(1.747)			123	0.094	0.069
Maximum number of words recalled in learning phase (mean(SD))	12.353(1.353)	11.909(1.446)			145.5	0.277	0.038
BPRS positive symptoms (mean (SD))	1.990(0.881)	2.575(1.592)			148	0.293	0.025
BPRS negative symptoms (mean (SD))	2.245(0.593)	2.575(1.202)			171	0.663	0.004
PANSS positive symptoms (mean (SD))	1.550(0.556)	1.883(1.158)			184.5	0.947	<0.001
PANSS negative expressive (mean (SD))	2.476(0.741)	2.709(1.100)			171	0.671	0.004
PANSS negative amotivation (mean (SD))	2.882(0.985)	3.091(1.319)			179	0.829	0.001
SIPS disorganisation (mean (SD))	0.546(0.513)	1.500(1.452)			90.5	0.033	0.103
SIPS positive (mean (SD))	2.135(0.795)	2.550(1.091)			142.5	0.603	0.006
SIPS negative (mean (SD))	0.812(0.698)	1.420(1.692)			128.5	0.351	0.020

Significant values after Benjamini-Hochberg correction at the 0.026 level are displayed in **bold**

3.4. Neuroimaging

When comparing the volume of hippocampal subfields in subjects divided according to the trajectory of raw verbal memory retention (N-High=21 vs N-Low=14), we did not observe any significant difference neither in left or right global hippocampal volume nor in the volumes of any hippocampal subfield ($p > 0.07$). However, when comparing subjects divided according to the trajectory of normalized verbal memory retention (N-High=27 vs N-Low=8), patients with

steeper memory decline presented significant reductions of both the left (p = 0.039, g = 0.76) and right (p = 0.021, g = 0.95) global hippocampal volume (see Supplementary materials, Figure S2). Such global decline was driven by significant reductions at the level of the bilateral CA3 (p_left = 0.047, g_left = 0.80, p_right = 0.01, g_right = 0.92), CA4 (p_left = 0.023, g_left = 0.95, p_right = 0.008, g_right = 1.1), dentate gyrus (p_left = 0.032, g_left = 0.92, p_right = 0.009, g_right = 1.1) and molecular layer (p_left = 0.015, g_left = 0.84, p_right = 0.012, g_right = 1.1), as well as left CA1 (p = 0.021, g = 0.67) and right subiculum (p = 0.029, g = 0.81).

4. Discussion

The overall aim of the present study was to investigate verbal episodic memory processes and to further characterize the consolidation of memory in a population at high risk of cognitive deficits and psychopathology. By exploring memory performance on longer delays than standardized memory testing batteries (one day, one week, one month), we set out to shed further light on abnormal memory consolidation patterns in 22q11DS compared to a control population. Overall, although reported as a relative strength in 22q11DS, when tested on delays exceeding thirty minutes, verbal memory processes were impaired, providing first evidence for an ALF in this population.

4.1. Evidence for an accelerated long-term forgetting when compared with controls

4.1.1. Comparable learning performance

We showed that in a verbal episodic memory task, participants with 22q11DS acquired the same amount of words and at the same pace than the control group. This is in line with previous work showing preserved verbal encoding in 22q11DS (Debbané et al., 2008). Furthermore, studies using global memory batteries showed that participants with 22q11DS obtained immediate verbal memory scores that were in the normal range (L. E. Campbell et al., 2010;

Lajiness-O'Neill et al., 2005). Together these results suggest preserved verbal learning performance in this population.

4.1.2. Shape difference in memory trajectories through time

When trajectories were examined through time, we found a significant shape difference between groups. Indeed, our results showed similar memory performance between groups at the standard delay of thirty minutes after the learning phase, but on longer delays, a significant drop in performance was observed in the 22q11DS group, suggesting abnormal consolidation processes. Thus, our first hypothesis of an ALF phenomenon in this population was supported. This finding has important conceptual and clinical implications, as it challenges the current literature on verbal long-term memory. Indeed, until now, consolidation processes were typically considered to be preserved in 22q11DS, since immediate recall and thirty minutes delayed recall were found to be in the normal range (Lajiness-O'Neill et al., 2005). Using adapted tools for the assessment of long-term consolidation processes, we were however able to demonstrate a considerable ALF phenomenon that has been overlooked thus far and may involve underestimated educational or daily life challenges for affected individuals. These results highlight how current clinical assessment tools should be adapted to fully grasp memory processes in this population (Elliott et al., 2014). It also brings considerations around clinical patient management and future intervention targets tailored to this population. Indeed, educational and professional arrangements, such as limiting the amount of information to be memorized by heart and provide with memory aids, or regular reminders of previously learned information, could be useful.

4.1.3. Recognition processes

To our knowledge, this is the first paper to compare recall and recognition performance in one single design. When recognition memory performance was examined though time, we observed a similar pattern of decline as for recall performance. Post-hoc analyses however indicated that

the decline in recognition performance was significant after a delay of thirty minutes and one month. From these results, one might infer that familiarity processes are weaker in 22q11DS. This conclusion would be in line with previous research showing deficits in source monitoring (Debbané et al., 2008). Thus, we have shown for the first time similar patterns of decline in recall and recognition performance in this population.

4.1.4. Lack of improvement with age in the 22q11DS group

When we examined the influence of age on long-term memory processes, we did not find any correlation with age in the 22q11DS group. This result contrasts with a positive correlation between age and performance in the control group, with older individuals performing better at the memory task. One possible explanation for this result is that verbal long-term memory skills do not evolve as drastically with age as in typically developing individuals. Therefore, young participants may perform similarly to older participants. These results could suggest that performance reach a developmental plateau much faster than the control group. To our knowledge, although similar results have been previously shown for other cognitive domains (e.g. executive functions) in this population (Maeder et al., 2016), this question has never been investigated in the field of verbal long-term memory. Future studies should examine developmental trajectories of verbal long-term memory in 22q11DS.

4.2. Subgroups of memory patterns in the 22q11DS population

As for the second aim, our results showed that trajectories of verbal long-term memory were heterogeneous, in line with the literature describing a vast phenotype in 22q11DS (Philip & Bassett, 2011; Swillen & McDonald-McGinn, 2015). We used a cluster analysis with two different approaches to identify subgroups in this population.

In the first approach, raw long-term memory scores were used, since learning competences in the 22q11DS group were similar to those of controls. We extracted two subgroups with high and low long-term memory competence, respectively. Interestingly, the group with higher long-

term memory performance had a long-term memory trajectory resembling the curve of the control group. Conversely, the group with lower long-term memory had a significantly steeper decline in performance with time. These results suggest that there is a subgroup of participants driving the ALF effect that was observed in the comparison against controls. This subgroup with lower long-term memory also exhibited lower IQ and higher rates of positive psychotic symptoms. As measures of IQ rely partially on memorized information (Wechsler, 2011), this association was expected. Regarding the association of poor verbal long-term memory and psychotic symptoms, cognitive decline has been identified as a risk of developing a psychotic illness in 22q11DS (Vorstman et al., 2015). Nevertheless, previous studies have shown similar levels of intellectual functioning in a population affected by 22q11DS with predominant negative symptoms compared to a population having low levels of symptoms (Schneider, Van der Linden, et al., 2014). Thus, consistent with our results, positive symptoms rather than negative seem to be more related to cognitive deficits, especially for memory processes. Moreover, a study on hippocampal development in a partially overlapping sample of patients with 22q11DS demonstrated that only positive symptoms are correlated with hippocampal volume decrease during adolescence (Mancini et al., 2019).

To deepen our understanding of memory processes in these subgroups, we examined trajectories of memory recognition over time. We found a pattern comparable to recall performance, with lower recognition competences in the group with lower global memory performance. Again, previous work has already shown in a different task that familiarity (depending on source monitoring) is a weak point in this syndrome (Debbané et al., 2008). This brings additional evidence for a disappearance of the memory trace with time and suggests that low scores on long-term memory are not caused by difficulties in the retrieval process of memory traces.

As the first clustering approach yielded a slight (although insignificant) difference in learning performance between both 22q11DS groups (HIGH vs. LOW), we conducted a second cluster analysis after normalizing long-term memory performance for learning. This procedure allowed us to directly isolate the consolidation processes at stake in this task and prevented potential biases due to differential learning performances. Clustering also yielded two subgroups with significantly different long-term memory performance. More specifically, using the normalized memory performance as a clustering input, we found a smaller subgroup of patients with lower long-term memory performance who exhibited an unexpected long-term memory trajectory. Interestingly, this subgroup had a significant drop already visible after a delay of thirty minutes, which does not typically qualify as an ALF phenomenon. These results suggest that although these individuals were able to learn the words that were presented, consolidation (short-term and long-term) processes did not occur properly, leading to the gradual disappearance of the trace in memory. Furthermore, this subgroup with less efficient consolidation had a significantly lower IQ than the other 22q11DS subgroups and a trend to higher positive disorganization symptoms. As mentioned before, numerous aspects of intelligence are evaluated through previously memorized knowledge (especially in the verbal scales), and the association between poor memory performance and IQ is therefore not surprising. Moreover, as the participants in this group also exhibited memory loss on shorter delays (thirty minutes), lower scores on general intelligence could be expected. As for the larger group with higher long-term memory performance, it was characterized by a pattern of forgetting that resembled controls. Finally, we compared recognition memory trajectories in both clusters to further understand performance in these groups. Results were very similar to the ones obtained in the first clustering procedure. Indeed, the subgroup with lower performance on recall through time also had poorer recognition performance with scores dropping rapidly through time. Again,

these results converge to poorer memory performances that are neither supported by familiarity nor recollection.

4.3. Neuronal correlates of verbal memory performance in 22q11DS

As for our third aim, when clustering patients according to raw memory scores, we did not find any difference in hippocampal anatomy between groups. However, when normalizing retention scores for learning, the subgroup of patients presenting both short-term and long-term accelerated memory decline presented significant smaller bilateral hippocampal volume driven by largely symmetric volumetric reductions affecting several hippocampal subfields, including CA3, CA4 and dentate gyrus. Hippocampal differences were observed only when normalizing for learning and remained significant after controlling for overall cognitive performance. This suggests that hippocampal alterations may specifically affect memory consolidation. This finding is in line with previous work on the hippocampus showing that this cortical structure is essential for the early phases of memory consolidation (Frankland & Bontempi, 2005). Difficulties in the learning phase are, on the other hand, more likely related to other neurodevelopmental alterations previously described in 22q11D.2S, such as accelerated cortical thinning, or altered structural and functional cortical connectivity (Padula, Schaer, Scariati, Maeder, et al., 2017; Scariati et al., 2016; Schaer et al., 2009). More specifically, the earliest working-memory phase of memory acquisition largely depends upon fronto-parietal cortical networks, and connectivity alterations of this network have been specifically related to working memory deficits in 22q11DS (Sandini et al., 2018). Thus, while fronto-parietal anomalies are likely related to impairments in the learning phase of memory processes, hippocampal anomalies appear to be specifically associated to altered memory consolidation, visible in our sample through an accelerated memory decline starting from thirty minutes post-acquisition.

4.4. Limits and future directions

This study comes with some limitations. First of all, the age-related data presented here is from a cross-sectional approach, with a relatively large age range. However, in order to identify specific developmental patterns that could inform us on the outcome of our participants, a follow-up study with longitudinal data on memory consolidation could be very useful.

Secondly, the neuroimaging approach we used in this paper only allowed us to make an indirect link between verbal long-term memory consolidation performance and brain structures. But as memory consolidation is believed to be a dynamic process, structural imaging may not be sufficient to capture difference between subgroups. Indeed, future research could add a combination of cognitive tasks with functional magnetic resonance imaging (fMRI) to further understand the processes at stake.

Thirdly, to measure episodic memory, we used a word-list task that is lacking ecological value. Although this task is the most commonly used to assess episodic memory in an experimental setting and is used as a proxy for everyday memory, we cannot be entirely certain that the processes at stake are the same inside and outside of the experimental setting. Future studies should focus on the development of more ecological measures to assess episodic memory in this population.

Fourthly, the size of our sample is acceptable for diagnostic group comparisons (22q11DS vs. typically developing controls) but both groups are not completely homogenous. For example, as mentioned before, the age range used in this paper is very large and developmental processes are difficult to capture in this setting. Once again, a follow-up study with longitudinal data could be very useful to disentangle the developmental dynamic of memory processes. Furthermore, even if it is a rare genetic disease, the phenotype of 22q11DS is very heterogeneous and research on this population tends to require a stratification of patients. Here we used a clustering method to stratify the sample. This had the consequence to reduce the sample size for the within

diagnostic group comparison and in the neuroimaging analyses and therefore decrease statistical power. This should be considered in the interpretation of our results.

Finally, there is a growing literature about the role of sleep on memory consolidation (e.g., Wilhelm, Prehn-Kristensen, & Born, 2012) that was not taken into account in this study. As sleep disturbances (e.g., sleep apnea) are more frequent in 22q11DS than in the normal population (Kennedy et al., 2014), the quality of sleep and the influence of sleep disturbances on long-term memory consolidation performance should be investigated.

5. Conclusion

In conclusion, this study tested the hypothesis of disrupted verbal long-term memory consolidation in 22q11DS and revealed the existence significant impairments compared to controls when delays longer than thirty minutes were examined. Furthermore, we characterized the heterogeneity of memory performance by dividing individuals with 22q11DS into subgroups by dividing into subgroups and identified a subgroup with low performance in memory recalls already at a delay of thirty minutes. This subgroup also had a significant reduction of volume in different hippocampal subfields and was associated with a more severe outcome (intellectual disability and higher disorganized psychotic symptoms). These results revealed different patterns of verbal long-term memory over time in the 22q11DS group, which should be considered in the development of cognitive intervention programs and for caregivers.

Study 4 - Specific deficit to retrieve remotely acquired memories in patients with 22q11.2 deletion syndrome[4]

Abstract

Background: Higher rates of forgetting of verbal information was recently highlighted in 22q11.2 deletion syndrome (22q11DS) when memory retention was tested over delays longer than thirty minutes. However, it is yet not clear whether increased forgetting in patients compared to controls reflected deficits in retrieval of memories acquired remotely (long delays) or if this population is more susceptible to interference during memory reconsolidation occurring at each recall. This study examines retention in verbal and non-verbal memory over a one-month delay, with and without potential interference through reconsolidation.

Methods: 48 participants (24 with 22q11DS) completed an episodic memory task that required participants to recall information over delays of thirty minutes and one month (partial design) or over delays of thirty minutes, one day, one week and one month (full design). Testing was done from a far by videoconference, and both verbal and non-verbal memory were examined.

Results: Comparing memory retrieval between groups, significantly lower percentages ($p \leq 0.001$) were found after one month in the 22q11DS group (verbal and non-verbal) compared to healthy controls. No differences were found after thirty minutes. Comparing performance with and without intermediate retrievals (full vs. partial design) within each group, significantly lower retention percentages after one month were found in the absence of intermediate retrievals, and these differences were particularly pronounced for 22q11DS ($p \leq 0.001$; $p \leq 0.01$ for control participants).

Conclusion: This study confirms and extends results on faster forgetting in 22q11DS for verbal and non-verbal material after a delay of one month. Comparing task designs reveals that in

[4] This study is a reprint of the article: Maeder, J., Schneider, M., Caroni, P., Kliegel, M., & Eliez, S. (under review). Specific deficit to retrieve remotely acquired memories in patients with 22q11.2 deletion syndrome.

22q11DS retrieval of memories remotely acquired is majorly impaired, and that intermediate retrievals prevent faster forgetting in 22q11DS.

Introduction

The ability to retain and recall memories over time is supported by two key brain structures, the hippocampus and prefrontal cortex (PFC), which roles are complementary in memory processing (Eichenbaum, 2017; Euston, Gruber, & McNaughton, 2012). Immediately after learning, activation in the hippocampus is high, whereas the engagement of PFC is very low; as the memory trace matures, the level of engagement of the structures reverse and the PFC becomes more activated than the hippocampus during retrieval of remotely acquired memories (Eichenbaum, 2017; Frankland & Bontempi, 2005; Preston & Eichenbaum, 2013). Within this framework, recalling distant memories requires long range interactions between hippocampus and PFC.

In chromosome 22q11.2 deletion syndrome (22q11DS), a genetic condition known for its increased risk for developing psychosis and specific cognitive deficits, both brain structures show structural and functional abnormalities (Rees et al., 2014; Rogdaki et al., 2020; Swillen & McDonald-McGinn, 2015). Indeed, diminished volume of the hippocampus has been consistently reported (Debbané et al., 2006; DeBoer et al., 2007; Kates et al., 2006; Mancini et al., 2019; Scott et al., 2016). As for PFC, excessive cortical thinning of frontal regions during adolescence has been demonstrated in 22q11DS, pointing toward altered brain maturational processes in this population (Ramanathan et al., 2017; Schaer et al., 2009). In addition, 22q11DS exhibits an impairment of long-range connectivity for frontal and midline structures (Scariati et al., 2016). Furthermore, disrupted long-range synchrony between the hippocampus and PFC have been demonstrated in a mouse-model of 22q11DS (Sigurdsson et al., 2010). In

light of these results, retrieval of remotely acquired memories could be compromised in this population because of a lack of synchrony between structures.

Standardized tasks available and usually applied for clinical purposes and research, limit the assessment of memory to delays of thirty minutes, yielding only a partial understanding of memory retention, and no information on remotely acquired memories. Indeed, when examined upon delays of thirty minutes, mild non-verbal memory impairments have been reported in 22q11DS, whereas verbal memory appeared to be less affected, or even preserved (L. E. Campbell et al., 2010; Lajiness-O'Neill et al., 2005). However, in a study investigating forgetting (using a directed forgetting paradigm), Debbané et al. (2008) showed that adolescents and young adults with 22q11DS experience difficulty suppressing irrelevant verbal information during retrieval, leading to memory dysfunction.

In a recent study, we challenged the current view of spared verbal memory by exploring memory retention over longer delays, up to one month (Maeder et al., 2020). The results revealed evidence for accelerated forgetting of verbal material over time, compared to a control group. By adding supplementary delays (one day, one week and one month), we explored the dynamic of forgetting. Despite comparable learning rates and similar percentage of information retained after thirty minutes compared to controls, the results showed a significant reduction of the percentage of information retained in the 22q11DS group after delays of one day, one week and one month. Furthermore, for 22q11DS participants, the percentage of information retained dropped significantly between each time delay.

While the results from this study demonstrated faster forgetting in 22q11DS participants, it remained unclear whether the higher rates of forgetting were the result of impaired retrieval of remotely acquired memories, or whether they reflected increased interference through reconsolidation processes. Consolidation of information in memory occurs through a dynamic process of strengthening and stabilization of synaptic connections (Bisaz et al., 2014; R. E.

Clark & Martin, 2018). During retrieval, as connections are reactivated, the memory trace is in a transient labile state, susceptible to change before reconsolidating (Alberini & Ledoux, 2013). At that moment, the memory trace can be either weakened and disrupted or enhanced and associated to other parallel traces. According to the reconsolidation view, memories are retrieved in the last version stored during the previous retrieval rather than as the original experience. As such, reconsolidation has been considered by some authors as memory updating. When these considerations are applied to our previous study, every time we asked participants to remember what they had learned, the memory trace was brought back to a labile state, susceptible to change (weakening or enhancement). By multiplying recalls over four different delays, we increased the possibility that the original trace would be modified. In healthy participants, following the notion of *testing effect*, retrieval of information from memory enhances retention over time, particularly when it requires effortful processing (i.e., free recall instead of recognition) (for a review see Roediger & Butler, 2011). In this way, it is believed that more frequently reactivated traces are strengthened and those less reactivated are forgotten (Frankland, Köhler, & Josselyn, 2013). However, for the 22q11DS population, these processes have not been specifically investigated.

To examine retrieval of remotely acquired memories without interference of reconsolidation processes, we created another version of the task previously used in Maeder et al. (2020) by removing intermediate delays in time, and only keeping recalls after thirty minutes and one month. We hypothesized that, similarly to the initial study, we would find evidence for higher rates of forgetting. Indeed, we expect that after thirty minutes, comparable percentage of memory retention between groups would be observed, but after a delay of one month, significantly lower percentages would be found in 22q11DS.

To examine the impact of reconsolidation on forgetting rates after a one-month delay across designs, we compared performance in a sub-sample of participants on the initial design

including intermediate retrievals (full design) and the new design without intermediate retrievals (partial design). In line with the testing effect previously described, we hypothesized that fewer retrieval opportunities would influence performance at one month. More specifically, in the control group we expected lower retention percentage in the partial design compared to the original design due to lack of retrieval opportunities when intermediate recalls were removed. In the 22q11DS group, intermediate recalls might enhance remote retrieval like in controls, or they might interfere with retrieval, accounting for some of the findings on forgetting.

Methods

Participants

Forty-eight participants (24 with 22q11DS) from the longitudinal study on 22q11DS (Geneva Cohort) were asked to participate in a supplementary assessment on learning and memory done remotely following their last participation in the longitudinal study. As previously described (Cantonas et al., 2019; Maeder et al., 2016), for the 22q11DS group, the presence of the deletion is confirmed using quantitative fluorescent polymerase chain reaction (QF-PCR). In this sample, the control group was mainly composed of siblings to the affected participants (23/24; 95.83%) and one community control. Groups did not differ in term of age or gender (see Table1). All participants were initially recruited through advertisement in patient associations, newsletters and word-of-mouth. Written informed consent, based on protocols approved by the Ethical Committee of the Canton of Geneva (CCER, Switzerland), was obtained for all participants and their parents (if the participant was younger than 18 years old). Information on psychiatric comorbid disorders was not reassessed but provided from the extended psychiatric evaluation performed by a trained psychiatrist (SE) during the last visit in the longitudinal study (table 1). As already described in different previous studies (e.g., Maeder et al., 2016;

Schneider, Schaer, et al., 2014), participants with 22q11DS and their caregivers were interviewed by a trained psychiatrist using the computerized Diagnostic Interview for Children and Adolescents-Revised (DICA-R; Reich, 2000) or the Structured Clinical Interview for DSM-IV Axis I (SCID-I; First et al., 1996). Psychotic disorders and psychotic symptoms were assessed with the supplement of the Schedule for Affective Disorders and Schizophrenia for School-age children Present and Lifetime (K-SADS-PL; Kaufman et al., 1997). At time of evaluation, 7 (29.17%) participants with 22q11DS were taking medication that can affect cognitive performance (for details see Table 1). Typically developing controls were screened for learning disabilities, psychiatric illnesses and medication prior to inclusion in the Geneva Cohort.

Table 1 Participant characteristics

			Diagnostic group		Comparison		
			22q11DS	Controls	ANOVA	Pearson's Chi-square	p-value
N			24	24			
Gender (male(%))			7 (29.17%)	9 (37.50%)		0.375	0.540
Age (mean (SD))			16.74(5.39)	15.99 (5.12)	0.247		0.621
Interval in month between full and partial design (mean(SD))			25(14)	25 (9)			
Known psychiatric diagnosis (%)	Total		14(58.34%)				
	Categories	Psychosis	0(0%)				
		Attention deficit disorder	5(20.84%)				
		Simple phobia	11(45.84%)				
		Social phobia	2(8.34%)				
		Generalized anxiety disorder	6(25.00%)				
		Separation anxiety disorder	1(3.85%)				
		Major depressive episode	3(12.50%)				
		Obsessive-compulsive disorder	1(4.17%)				
		Oppositional defiant Disorder	0(0%)				
Medication at testing (%)	Total		7(29.17%)				
	Categories	Methylphenidate	3(12.50%)				
		Antidepressants	3(12.50%)				
		Antipsychotics	2(8.34%)				
		Antiepileptic	0(0%)				
		Anxiolytics	0(0%)				

Significant values at the 0.05 level are displayed in **bold**

Materials

The original memory task (full design) was created to examine acquisition and retention of information over time (Maeder et al., 2020). Participants were required to learn 15 common words and 15 signs (drawings made out of 1 or 2 basic geometrical forms). After delays of

thirty minutes, one day, one week and one month, participants were asked to freely recall the words and the signs they remembered.

In this study, we modified the design by eliminating intermediate recalls (partial design). In detail, we performed the learning phase as well as free recall and recognition after delays of thirty minutes and one month (see Figure 1). To maximize participation and accommodate families, the procedure was adapted to be done remotely by videoconference with Skype® (Microsoft, 2003). A large majority of participants (41/48, 85%) had previously completed the full design with all intermediate recalls. Twenty-nine (60.42%) were included in the sample from the previous study (Maeder et al., 2020). To ensure participants could complete the task several times without interference we created 4 parallel versions of equal difficulty. Version of the task was randomly balanced within each group (22q11DS and Controls), as well as modalities order (verbal and non-verbal first).

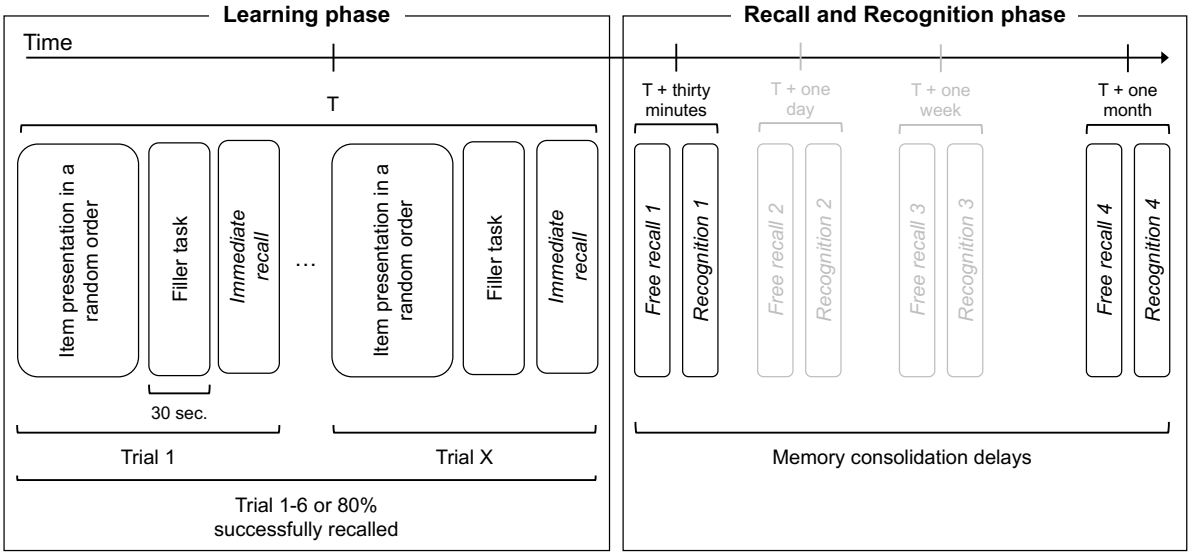

Figure 1: Adapted task design (partial design) to address the research question of memory consolidation. The original task design (full design) is shown in grey.

Procedure and variables of interest

For the verbal part of the task, the procedure was identical to the original task (full design). Briefly, fifteen words were read out loud by the examiner and then freely repeated by the

participant after a short backward counting task (e.g., 100-1; 100-2; 300-6) of thirty seconds. Words were read in a different randomized order at each presentation. Words were presented until the 80%-success criterion (12 items) was achieved, or a maximum of 6 trials. To adjust for different number of presentation trials, a *verbal learning score* was calculated by dividing the maximum number of words correctly recalled at any trial and the number of trials to reach criterion.

For the non-verbal part of the task, the examiner used the *share screen* option of the application to show the non-verbal stimuli. They were presented to the participant at a pace of 1 per 3 seconds on the screen. Before drawing them on a piece of paper, participants had first to look for 30 seconds at two similar scenes presented on the screen to find differences. Every trial, participants had to draw on a new piece of paper (not to be influenced by previous drawings) before showing the production to the examiner via the camera of the computer. Participants were instructed to dispose of the used paper (throw in the trash or remove from sight) in between learning trials. Again, the 80%-success criterion or a maximum of 6 trials was applied. A *non-verbal learning score* was again computed on the same model as the verbal task.

After a delay of thirty minutes after the end of the learning phase, participants were asked to remember the items they learned. The order of stimuli modality presented (verbal or non-verbal done first) was respected. Words were spoken out loud and signs were drawn on a blank piece of paper. Number of items produced and error rates were recorded. To correct for different learning performances across individuals and across modalities, a *retention percentage* was calculated instead of using raw scores. This was done by dividing the number of recalled items (after thirty minutes or one month) by the maximum number of items recalled during the learning phase. Errors in the verbal task both included *repetition errors* (words already produced), and *intrusion errors* (words that did not belong to the target collection). In the non-verbal task, errors included *object errors* (incorrect object, i.e., square instead of triangle), *space*

errors (incorrect location, i.e., a circle on top of a square instead of under the square), and any item that did not belong to the target collection or produced twice were qualified as *other errors*. Following free-recall, participants were asked to recognize the 15 targets among 15 distractors. However, in the scope of this paper, recognition was not analyzed.

Missing memory data

The dataset from the partial design was complete for all participant except two control participants. Indeed, one missed the one-month delay appointment (verbal and non-verbal information was not acquired) and for another participant, a technical failure occurred at the thirty minutes delay in the non-verbal part only.

Data from the same participants with the full task design was available for 41 individuals (20 with 22q11DS). Here, memory retention after a delay of one month was missing for 4 participants (1 with 22q11DS) for both verbal and non-verbal modality due to participants' unavailability at appointment. Non-verbal data for one control participant after one-month delay was missing due to technical failure in saving the production.

When checking the data for normality, 1 outlier was identified in the 22q11DS for the thirty minutes retention, non-verbal task, full design. Since the 5% trimmed mean value was very different from the mean value (Mean=103.594; Trimmed mean=96.408), indicating it had a lot of influence on the mean, this score was removed from the analyses. Results reported here do not include the outlier.

Statistical analyses:

As data did not always follow a normal distribution, we performed non-parametric statistics (Mann-Whitney test and Wilcoxon signed rank test) for between- and within-group comparisons. As the age range is very broad and no correction for age is possible in non-parametric tests, correlation of performance with age was examined using Spearman

correlation. Analyses were performed in SPSS 25 (IBM). Reported significative results sustained a Bonferroni correction for multiple comparison.

Results

Correlation with age

The relationship between age and performance was examined in each group separately, for both task designs (partial and full). Overall, we found no significant correlations between memory retention (thirty minutes and one-month delays) and age for 22q11DS or for control participants (see Table 2).

Table 2 Spearman correlation of learning and retention with age

			Age					
			22q11DS			Controls		
			r	*p*	After Bonferroni correction	*r*	*p*	After Bonferroni correction
Design	Partial	Verbal learning score	0.347	0.097	n.s.[a]	0.481	0.017	n.s.
		Verbal Retention thirty minutes	0.178	0.404	n.s.	0.417	0.043	n.s.
		Verbal Retention one month	-0.397	0.055	n.s.	-0.187	0.394	n.s.
		Non-verbal learning score	0.236	0.267	n.s.	0.603	0.002	sig.[b]
		Non-verbal Retention thirty minutes	-0.129	0.558	n.s.	-0.100	0.650	n.s.
		Non-verbal Retention one month	-0.384	0.064	n.s.	0.071	0.748	n.s.
	Full	Verbal learning score	0.367	0.112	n.s.	0.346	0.124	n.s.
		Verbal Retention thirty minutes	0.091	0.701	n.s.	0.377	0.092	n.s.
		Verbal Retention one month	0.143	0.559	n.s.	0.213	0.411	n.s.
		Non-verbal learning score	0.459	0.042	n.s.	0.717	0.000	sig.
		Non-verbal Retention thirty minutes	0.481	0.032	n.s.	-0.213	0.368	n.s.
		Non-verbal Retention one month	-0.365	0.124	n.s.	0.511	0.043	n.s.

[a]n.s. = non statistically significant
[b]sig = statistically significant

Between group comparison (22q11DS vs. Controls) in the partial design

Mann-Whitney comparisons (see Figure 2) revealed no significant between-group difference on memory performance normalized for learning after a delay of thirty minutes in the verbal (p=0.175), or the non-verbal parts of the task (p=0.698). However, after a delay of one month, compared to the control group, 22q11DS participants showed significantly lower retention performance in the verbal ($Mdn_{22qVerbal}$=29.021, $Mdn_{CtrlVerbal}$=50, U=124.500, z=-3.229, p=0.001, η^2=0.227), and in the non-verbal parts of the task ($Mdn_{22qNVerb}$=11.112, $Mdn_{CtrlNVerb}$=25, U=129.000, z=-3.134, p=0.002, η^2=0.214).

Error-rates did not significantly differ between groups, at any time delay (thirty minutes or one month), in any modality (*ps*>0.154).

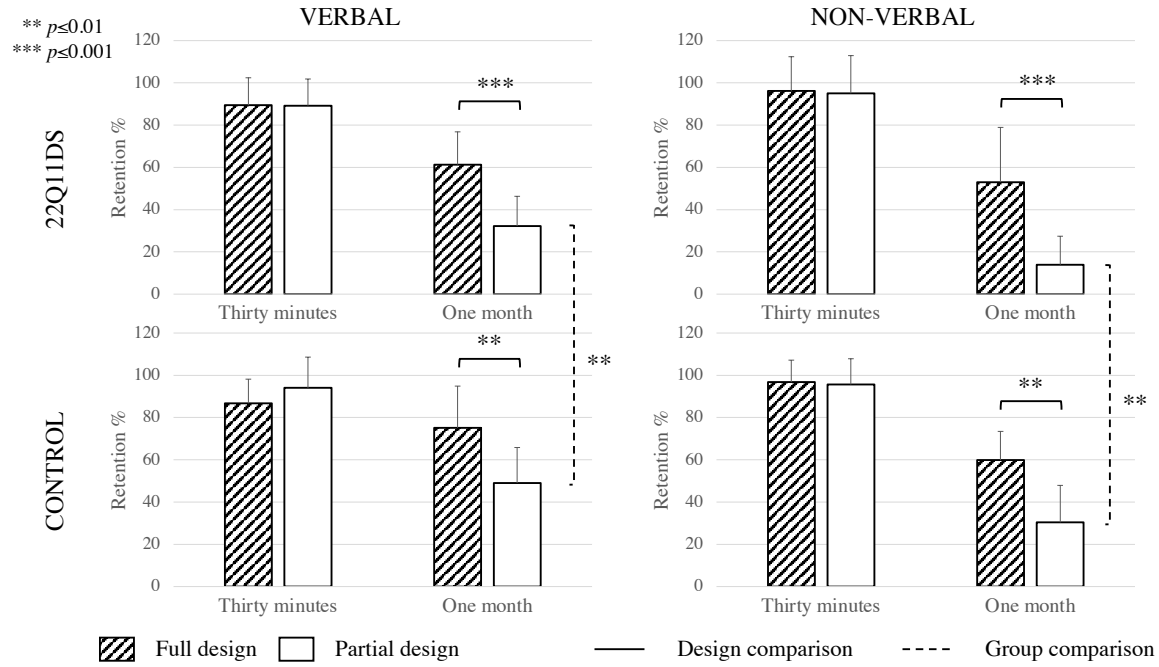

Figure 2: Percentage of memory retention over time (corrected for learning) between groups (22q11DS vs. Controls), across modalities (verbal vs. non-verbal) for each task design (full vs. partial). Only statistically significant design comparison (solid line) and group comparison in the partial design (dashed line) are shown in the figure.

Comparison of designs (partial vs. full)

We compared performance of learning and retention between designs using Wilcoxon signed ranks tests, separately in each group for both modalities. In the 22q11DS group, there was no significant difference in learning scores for verbal items (p=0.925) or non-verbal items (p=0.632). After a delay of thirty minutes, there was no difference in memory retention performance in the verbal task (p=0.653) and the non-verbal task (p=0.443) (see Figure 2). However, after a delay of one month, a significant difference was found between task designs with significantly lower percentages of items recalled in the verbal task ($Mdn_{1MonthPartial}$=29.021, $Mdn_{1MonthFull}$=65.500, Z=-3.823, p<0.001, η^2=0.812) and the non-verbal task ($Mdn_{1MonthPartial}$=11.112, $Mdn_{1MonthFull}$=46.154, Z=-3.823, p<0.001, η^2=0.812) in the partial design. In the control group, similar results were observed with no differences between learning

scores (verbal p=0.709; non-verbal p=0.712) or memory retention after a thirty minutes delay (verbal p=0.138; non-verbal p=0.394) (see Figure 2). Retention percentages after one month were significantly lower in the partial design for verbal ($Mdn_{1MonthPartial}$=50, $Mdn_{1MonthFull}$=76.923, Z=-2.856, p=0.004, η^2=0.510) and non-verbal items ($Mdn_{1MonthPartial}$=25, $Mdn_{1MonthFull}$=57.738, Z=-2.919, p=0.004, η^2=0.426) items.

Error-rates did not significantly differ between designs, at any time delay (thirty minutes or one month), in any modality for 22q11DS and control participants (ps>0.050).

Discussion

We have examined, for the first time, retrieval of remotely acquired memories, and the influence of memory reconsolidation on this process in 22q11DS. By removing intermediate recalls upon delays of one day and one week, memory retrieval was examined with minimal influence of reconsolidation processes. Evidence for higher rates of forgetting in the 22q11DS group was confirmed for verbal material and extended to non-verbal material. Notably, the design with multiple recalls over time benefited all participants compared to the partial design.

First, the results from the partial design replicate and extend previous findings using the full task design showing increased levels of forgetting in the verbal modality. Our results confirm the previous findings concerning reduced retrieval at one month in the 22q11DS group (Maeder et al., 2020), and extend those findings to the non-verbal modality, which was even more strongly affected. In light of these findings, adapted assessment tools should be developed, and used to identify 22q11DS patients who could benefit from cognitive training targeting memory consolidation.

Secondly, when retention percentages were compared between designs (partial vs. full), the results yielded a more important forgetting rate in the partial design, where intermediated recalls were removed. In line with our hypothesis, this finding suggests that multiple recalls

across time help stabilizing the memory trace over long delays. This significant difference between designs was observed in the control group, but even more so in 22q11DS, indicating that both groups benefitted from reconsolidation. Our result that multiple recalls over time slow down forgetting in 22q11DS bear important practical implications for educational strategies that should be considered when working with affected individuals.

Finally, comparing error rates between designs did not yield any significant difference in neither group. Adding to the previous conclusions, the significant difference between both designs reflects forgetting due to a decay of the memory trace, shown by less items produced, rather than an interference which would manifest by an increase in confusion errors (word intrusion errors, sign object and space errors).

Limitations

First of all, using videoconference to acquire data made the testing environment more difficult to control for and more prone to distractibility than the lab environment. This was especially true for young children with 22q11DS, and around 21% of participants with 22q11DS met diagnosis for attention deficit disorder. However, support or supervision of the parents or an older sibling helped the participants to stay engaged in the activities. All tasks were completed until the end, and the rules were easily respected by all participants. Overall, videoconference proved to be of great help in order to accommodate the schedules of the families, which in turn maximized participation rates.

Secondly, the sample size presented here is limited, and includes a broad age range. Due to the distribution of our sample, use of non-parametric tests prevented from adding age as a covariate in the analyses. However, groups were matched on age and results from correlations showed that memory retention over time is not correlated to age. A next step to ensure representativeness of the findings, should be to replicate these results on a larger independent sample.

Conclusion

In sum, by modifying the task design of a memory retention task, we examined the dynamic of forgetting over a delay of one month without the influence of reconsolidation processes. Our results confirm higher rates of forgetting already demonstrated in 22q11DS for verbal information and extend those findings to non-verbal information. Notably, our results reveal that intermediate retrieval events are at least as effective as in controls to counteract forgetting in 22q11DS. Our findings have clinical implications with respect to patient assessment tools, which should include evaluation of memory consolidation processes over delays longer than the standard thirty minutes. Furthermore, educational strategies should be adapted to include regular recalls in order to prevent the loss of important memories in 22q11DS patients.

Study 5 - Selective effects of methylphenidate on attention and inhibition in 22q11.2 deletion syndrome: results from a clinical trial[5]

Abstract

Background: Attention Deficit and/or Hyperactivity Disorder (ADHD) is the most prevalent psychiatric disorder in children with 22q11.2 deletion syndrome (22q11DS) and frequently persists into adulthood. Although medication with stimulant has been demonstrated to be highly effective in idiopathic ADHD, evidence in 22q11DS is still scarce. Previous studies have showed safety and effectiveness of methylphenidate (MPH) on core symptoms of ADHD as well as improvement of cognitive deficits associated. However, only on a limited number of cognitive domains have been explored.

Methods: Twenty-three participants with 22q11DS and attention difficulties, aged 8-24 years old, entered a clinical trial aiming to specify the effects of MPH on clinical symptoms, cognition and daily-life behavior. The effects of treatment were compared with/without medication in a within-subject design. The trial included both participants naïve to the molecule and chronic users.

Results: Benefit from the treatment was demonstrated through a decrease in core ADHD symptoms, specifically inattention symptoms, and improvement of cognitive measures of attention and inhibition. Conversely no significant change was found for other executive functions (such as cognitive flexibility, working memory, initiation), learning or memory. Moreover, no significant improvement on ecological measures of daily-life executive functioning was found, possibly because of the short treatment period. We replicated safety and although very frequent, side effects were of mild intensity and comparable to previous findings.

[5] This study is a reprint of the article: Maeder, J., Mancini, V., Sandini, C., Journal, F., Schneider, M., Kliegel, M., & Eliez, S. (under review). Selective effects of methylphenidate on attention and inhibition in 22q11.2 deletion syndrome: results from a clinical trial.

Conclusions: This study extends current knowledge on the effects of MPH in patients with 22q11DS. Treatment was found to be effective for core ADHD symptoms and cognitive measures of attention and inhibition.

Background

Attention Deficit and/or Hyperactivity Disorder (ADHD) is highly prevalent in neurodevelopmental disorders, including genetic syndromes (Lo-Castro, D'Agati, & Curatolo, 2011; Reilly et al., 2015). In chromosome 22q11.2 deletion syndrome (22q11DS), a collaborative study assessing over 1400 patients, found that ADHD is the most common diagnosis reported in children (37%) (Schneider, Debbané, et al., 2014). Furthermore, high rates of ADHD are also observed in adults (between 16-65%) confirming the persistence of this diagnosis with age (Antshel et al., 2013; Schneider, Debbané, et al., 2014). These rates largely exceed the prevalence of ADHD in the general population with meta-analyses showing 5.3% in children and adolescents, 2.5% in adults (Faraone et al., 2015).

The presentation of ADHD in 22q11DS is slightly different from idiopathic ADHD with higher rates of 22q11DS patients meeting the criteria for inattentive presentation (61-79% in 22q11DS vs. 38-57% in idiopathic ADHD) (Antshel et al., 2007; Niarchou et al., 2015; Schneider, Debbané, et al., 2014; Willcutt, 2012). Because of its nature, inattentiveness is more difficult to recognize than hyperactivity and impulsivity. Additionally even when symptoms are recognized they are sometimes "over-shadowed" by the low intellectual functioning which characterizes 22q11DS, delaying diagnostic and proper care (McDonald-McGinn et al., 2015; Reilly et al., 2015).

Treatment recommendation of ADHD for children from 5 years old includes medication with stimulants, methylphenidate (MPH) being recommended in first line (NICE guidelines, 2018). In idiopathic ADHD, extensive evidence show that MPH medication significantly reduces core

symptoms of ADHD compared to a placebo (Cortese et al., 2018; Faraone & Buitelaar, 2010). Additionally, cognitive domains (including attention and executive functions) consistently found to be impaired in ADHD, also show improvement with medication (Coghill et al., 2014; Swanson, Baler, & Volkow, 2011; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). Results from a meta-analysis, indicated that measures of non-executive functions, like memory, are also significantly helped by MPH (Coghill et al., 2014).

Despite high rates of ADHD in 22q11DS and the common prescription of stimulant, only two studies so far have investigated the safety and efficacy of MPH in this population (Gothelf et al., 2003; Green et al., 2011). In a first study, Gothelf et al. (2003) evaluated the effect of a low dose of MPH (0.3mg/kg) in 12 children and adolescents with 22q11DS and ADHD. They demonstrated a significant decrease of ADHD symptoms as well as improvement of cognitive measures of attention. Overall, after 4 weeks, treatment was well tolerated with no significant change in cardiac measures. Because 22q11DS constitutes an increased risk for developing schizophrenia (Rees et al., 2014), patients were also screened for psychotic symptoms, but no change was reported at follow-up. Side effects were very common (92%) but never severe enough to warrant discontinuation of medication. Similar to other studies on idiopathic ADHD, the most common reported side effect was poor appetite, but other effects were also relatively frequent (irritability, sadness, stomachaches, reduced talking with others and proneness to crying). Results are however limited by the small sample size (N=12) and the even smaller number of participants evaluated with cognitive measures of attention (N=6). In a second study, Green et al. (2011) extended previous findings by examining the effect and safety of MPH in 34 patients with 22q11DS and ADHD in a placebo vs. MPH design (respectively N=12 vs. N=22). In addition to the larger sample size, effect of MPH was compared to a placebo group on multiple cognitive measures, including 3 tasks measuring prefrontal cognitive functioning. After a single dose of 0.5mg/kg, the authors showed significant improvement in prefrontal task

performance (2/3 tasks improved). Safety and good tolerance to MPH was replicated. Participants reported similar rates of side effects immediately after medication and at the follow-up (6 months). Only 15 participants continued the MPH treatment for the entire 6 months period, but these participants showed a mean of 40% reduction in severity of ADHD symptoms (reported by parents with questionnaires). Altogether, these two studies suggest effectiveness and safety of MPH in 22q11DS. However, they provide only limited knowledge on the effect of MPH on cognitive measures for this population, as a limited number of domains of attention and executive function (EF) were explored. Therefore, the aim of this study was to investigate the benefit of a stimulant medication on a broader range of cognitive performance related to ADHD symptoms using a within subject design (with/without MPH). Effects were evaluated during 13 days of treatment in participants with a regular prescription of MPH and naïve to the molecule. As MPH has been shown to improve a broad range of attentional and EF domains in idiopathic ADHD (Nigg, 2005; Willcutt et al., 2005), we explored improvements of attention (selective and sustained), inhibition, cognitive flexibility, working memory, fluency and planning. Change in broader cognitive domains including learning and long-term memory was also explored.

Methods

This study aimed at investigating the effects of MPH on cognitive and clinical measures in 22q11DS patients. A within-subject design was employed to compare measures with/without MPH treatment. Depending on their medication history and current psychostimulant medication, participants were included either in the *consumer group* (participants with an ongoing treatment of MPH) or *naïve group* (participants naïve to the molecule).

Participants

Twenty-five participants (11 females) with 22q11DS, aged between 8-24 years old were enrolled in this study. They were recruited from the longitudinal cohort of 22q11DS patients (Geneva cohort). The presence of the deletion was confirmed using quantitative fluorescent polymerase chain reaction (QF-PCR) prior to inclusion in the Geneva cohort. Ethics approval and consent to participate is specified at the end of the manuscript.

For this study, inclusion criteria are the following:

1. Male or female with confirmed 22q11DS diagnosis.
2. Minimum age of 8 years or maximum age of 25 years and 11 months.
3. Attention difficulties pointed out by parents and/or the participant during the initial clinical interview.
4. Sufficient verbal expression and comprehension skills to understand and follow instructions based on initial interview.

Exclusion criteria for this study are:

1. Participants younger than 8 years and older that 25 years and 11 months.
2. Previous adverse experience with MPH.
3. Cardio-vascular diseases including rhythm disorders, severe hypertension, cardiac insufficiency, obliterating cardiac and peripheral arterial disease, preexisting cerebrovascular affections, hemodynamically significant congenital heart defect, channelopathies.
4. *For naïve participants*: corrected QT (QTc) distance at baseline electrocardiogram above 460 milliseconds or elongation at control electrocardiogram (Day 6 of treatment) superior to 30 milliseconds with functional complaint.
5. Psychiatric affections including anxiety attack, psychic tension or restlessness, manic episode, marked psychotic symptoms, schizophrenia, borderline personality disorder,

clinical depression (present or past), suicidal episode, diagnosis or family history of Tourette syndrome, alcohol or drug abuse.

6. Other somatic affections including hyperthyroid, glaucoma, pheochromocytoma.
7. Concurrent treatment with monoamine oxidase inhibitors or interruption less than 14 days before beginning of treatment.
8. Pregnancy or breastfeeding.

The total sample was composed of 16 *naïve* participants (6 females) and 9 *consumer* participants (4 females). Due to the inability to travel during the Coronavirus pandemic, two consumer participants (1 female) did not complete the second visit and were therefore excluded from the analyses. The final sample included 23 participants with at least 2 visits. Mean age at study inclusion was 14.46 (sd=5.22) years for the naïve group and 13.88 (sd=4.09) years for the consumer group.

Procedure

The evaluation was carried out by a trained psychologist and took place in person with some additional follow-up via videoconference the next day and one week later. All consumer participants had a prescription of Concerta®, although this study was intended as open-label. Concerta® is rapidly absorbed and reaches a first maximum in plasmatic concentration after 1 to 2 hours after oral administration (https://compendium.ch and Banaschewski et al., 2006). The plasmatic peak is reported to be between 6-8 hours after oral administration. Considering this, all evaluations done with MPH were conducted between 1.5 and 8 hours after oral administration to ensure coverage of the treatment. In the naïve group, the first visit served as baseline (without MPH) and the second assessed changes with MPH. In the consumer group, first visit was randomly assigned with/without treatment (3 participants started by visit with MPH) and second visit was planned accordingly. To limit learning effects of the cognitive measures, parallel task version with comparable difficulty were used for learning and memory

assessments. Additionally, a period of at least 1 month was required between visits with/without MPH. Mean interval between visits was 65.17 days (sd=32.07; minimum=35; maximum=134).

Treatment in the naïve group

Naïve participants were prescribed 13 days of Concerta® at a weight-adjusted dose of 0.7mg/kg, following 5 weight-categories (see Table 1). Except for participants lighter than 30kg (*N*=2), the treatment phase began with a lower introduction dose for 5 days before increasing to the weight-adjusted dose.

Table 1: Methylphenidate dosage per weight category

Participants *N*	Weight category	Dosage day 1-5	Dosage day 6-13
2	< 30kg	18mg	18mg
7	31-45kg	18mg	27mg
3	46-60kg	18mg	36mg
4	61-75kg	27mg	45mg
0	>76kg	36mg	54mg

Total = 16

Effect of treatment on cognitive measures was evaluated on Day six with a follow-up on memory on Day seven and thirteen. Effect of treatment assessed with clinical measures and questionnaires was conducted at the end of the treatment phase to guarantee several observation opportunities for the participant and the caregivers.

Treatment in the consumer group

For the visits with MPH, participants were asked to take their usual prescription. Mean dosage of MPH for the consumer group was 0.67mg/kg (sd=0.20; minimum=0.34; maximum=0.93), roughly comparable to the naïve group.

In order to follow the naïve group procedure as closely as possible, for visits without MPH, consumer participants were asked to interrupt their usual prescription for 13 days. Since many participants usually have a break in treatment during holidays or weekends, compliance high. For visits without MPH, a wash-out period of 5 days prior to evaluation with cognitive measures was asked of each participant. Again, to guarantee several observation opportunities for the

participant and the caregivers, assessments with clinical measures and questionnaires were done at the end of the interruption (Day thirteen).

Material

Outcome measures were chosen to evaluate ADHD through different aspects: clinical symptoms; cognitive tests of attention, EF, learning and long-term memory; questionnaires on daily-life behavior. For the naïve group, tolerance to treatment was examined though the report of side effects (quality, quantity, severity).

Clinical symptomatology

To appreciate the intensity of ADHD symptomatology and change with/without MPH, caregivers were interviewed on the 18 symptoms from the ADHD section, criteria A, of the Diagnostic and Statistical Manual of Mental Disorders – fifth edition (DSM-V; American Psychiatric Association, 2013). Presence of each symptom was evaluated with the following scale: 0=no information; 1=not present; 2=subclinical, behavior occurs sometimes with minimal impact on global functioning; 3=clinical, behavior occurs frequently with moderate to severe impact on global functioning. A global sum of symptoms intensity was computed, as well as a sum of inattention symptoms severity and a sum of hyperactivity/impulsivity symptoms severity. Assessment was available for 20 participants (16 naïve and 4 consumer).

Cognitive measures

A large selection of cognitive measures was chosen to evaluate the following domains: attention (Conners' Continuous Performance Test 3rd edition, CPT3, Conners and MHS Staff, 2014), inhibition (Stroop task, Albaret and Migliore, 1999; Stop-Signal Task, Cambridge Cognition Ltd., 2013), cognitive flexibility (Color Trails Test, D'Elia and Satz, 1989; Williams et al., 1995; Intra-/Extra-Dimensional Shift task, Cambridge Cognition Ltd., 2013), updating (Digit span and Letter-number sequencing, Wechsler, 2004, 2011); Spatial Working Memory task, Cambridge Cognition Ltd., 2013), initiation (Verbal and Non-verbal fluency task, Sevino,

1998), planning (Tower of London, Culbertson and Zillmer, 1999), processing speed (Coding and Symbol search, Wechsler, 2004, 2011), learning and long-term memory (modified 15 words and 15 signs, Maeder et al., 2020), for details see Table 2.

Table 2: Cognitive measures, description and interpretation

Domain	Test name	Variable	Description and interpretation
Attention	CPT-3	Detectability	Measure of how well the respondent discriminates non-targets (i.e. the letter X) from targets (i.e. all other letters). A high score indicates inattentiveness.
		Omission	Missed targets. A high score indicates inattentiveness.
		Commission	incorrect responses to non-targets A high score indicate impulsivity.
		Perseveration	Responses made in less than 100 ms. following the presentation of a stimulus. A high score is related to impulsivity.
		Hit Reaction Time (HRT)	Mean response speed in ms. Atypically slow HRT indicate inattentiveness. A very fast HRT combined with high commission errors rates indicates impulsivity.
		Hit Reaction Time Standard Deviation (HRT SD)	Consistency of response speed to targets. A high score indicates inattentiveness.
		Variability	Amount of variability the respondent showed in 18 separate sub-blocks of the administration in relation the overall HRT SD score. High variability indicates inattentiveness.
		Hit Reaction Time Block Change (HRT Block Change)	Slope of change in HRT across the 6 blocks of the administration. A positive slope indicates decelerating HRT suggesting loss of sustained attention.
		Hit Reaction Time Inter-Stimulus Intervals Change (HRT ISI Change)	Slope of change in reaction time across the 3 ISIs (1, 2, and 4 seconds). Positive slope indicates decelerating HRT at longer intervals suggesting loss of vigilance
Inhibition	Stroop	Inhibition ratio	Cost of inhibition. Calculated by dividing the number of colors named in the interference condition (naming the color of the ink of the word for 45 seconds), by the number of colors named in the color denomination condition (naming rectangles of colors for 45 seconds). Value closer to 1 indicate better inhibition.
	Tower of London	Rule violation	Failure to follow rules including type I (more beads than expected on a stick) and type II (move more than one bead at the time) errors. A high score indicates poor inhibition.
	Stop-Signal Task (CANTAB) [1]	Stop-Signal RT	Estimate of the length of time between the go stimulus and the stop stimulus at which the participant is able to successfully inhibit his response on 50% of trials. A high score indicates poor inhibition.
Cognitive flexibility	Color Trail Test	Flexibility ratio	Cost of flexibility. Calculated to account for processing speed by dividing the time to complete part B (drawing a line between number following chronological order while alternating between colors) by time to complete part A (drawing a line between number following chronological order). Value closer to 1 indicate better flexibility.
	Intra-Extra-Dimensional (CANTAB)	Extra-Dimensional Shift (EDS) errors	Number of extra-dimensional shift errors. A high score indicates poor flexibility.
Updating	Digit span	Backward span	Longest sequence of numbers repeated in reverse order. A low score indicates poor updating.
	Letter-Number sequencing	Letter-number span	Longest sequence of letters and numbers correctly ordered. A low score indicates poor updating.
	Spatial Working Memory (CANTAB)	Between Errors (4 Boxes)	Number of times the participant revisits a box in which a token has previously been found. Three different memory loads (4, 6, 8 boxes). A high score indicates poor updating.
		Between Errors (6 Boxes)	
		Between Errors (8 Boxes)	
Initiation	Verbal fluency	Number of animals produced	Number of different animal names produced under one minute. A low score indicates poor initiation.
	Non-verbal fluency	Different items produced	Number of different designs produced under three minutes. A low score indicates poor initiation.
Planning	Tower of London	Total moves	Number of moves beyond the minimum number of moves required to reach the goal position summed over all problems A high score reflects poor planning.
Processing speed	Coding	Number of codes produced	Raw score of items correctly reproduced. A low score indicates poor processing speed.
	Symbol Search	Number of symbols identified	Raw score of items correctly identified (either recognized or with a yes/no answer). A low score indicates poor processing speed.

Learning and long-term memory	Modified 15 signs and 15 words[2]	Learning score	Maximum number of items correctly recalled during learning divided by the number of trials to reach learning criterion. Low score indicates poor learning.
		Retention % (thirty minutes, one day, one week)	Number of items recalled after each delay in time divided by the maximum of items recalled during learning. Low score indicates poor memory.

[1]Detailed descriptions of the tasks can be found on the CANTAB website (https://www.cambridgecognition.com).
[2]All variables of the modifies 15 signs and 15 words exist in verbal and non-verbal modality

Different types of tools were used (paper/pencil, computerized tasks) in different modalities (verbal and non-verbal). Three computerized tasks came from the computer-interfaced Cambridge Neuropsychological Test Automated Battery (CANTAB). Due to an update, two different systems were used: *Research suit* and *Connect*. To ensure continuity, each participant was examined with the same system throughout all visits. For 21 participants (91.3%) tests were administered in the Research suit system using the CANTABeclipse version 6, on a portable touch-screen tablet running on a Windows-based PC system. For the remaining 2, tests were administered with an IPad® via the Connect web-based platform.

Questionnaires

Daily-life behaviors were assessed with the *Behavior Rating Inventory of Executive Function (BRIEF),* children and adult version (Gioia et al., 2000; Roth, Isquith, & Gioia, 2002). This questionnaire provides an ecological assessment of EF, with a Global Executive Composite (GEC) score derived from the Behavioral Regulation Index (BRI) and Metacognitive Index (MI). The BRI includes subscales of *Inhibition*, *Shifting*, *Emotional regulation* and only in the adult-form, *Self-monitoring*. The MI includes subscales of *Initiation, Working memory, Planning, Organization* and *Monitoring.* Observations are reported using standardized scores (T-scores). A T-score ≥65 is considered as pathological. To increase the sample for paired comparisons, the children and adult version were combined by using T-scores only. As a result, the Self-monitoring subscale from the adult version was not included in the analyses. Analyses were based on the assessment from caregivers (other-reported) available for 23 participants. Five adult 22q11DS participants also completed the self-reported version of the questionnaire, built on the same structure. This information was used in a complementary qualitative analysis.

Safety and tolerance to treatment (only naïve group)

An electrocardiogram was performed prior to the beginning of treatment (<3 month) to check QTc at baseline and repeated on *Day six* of treatment to evaluate possible change due to the treatment.

Regarding tolerance, observations from the participant and caregivers were compiled during the treatment phase through a home-made questionnaire sent by email or filled out with the examiner. Information was collected about the time treatment was taken, eventual missed treatment, side effects and intensity of eventual side effects. The questionnaire was completed on three occasions: end of *Day one* of treatment, *Day six* of treatment (when the dosage is increased for participants heavier than 31 kilos), end of the last treatment day (*Day thirteen*).

Evaluation of side effects was inspired by Barkley Side Effect Rating Scale (Barkley, Fischer, Newby, & Breen, 1988). Side effects were regrouped in 7 different categories: gastro-intestinal (including stomachache, nausea, decreased appetite), sleep disturbances (including difficulties falling asleep, insomnia, tiredness), neurologic (including headache, tremors, tics or nervous movements), cardio-vascular (including heart palpitations, dyspnea), mood (including sadness, withdrawal), other psychiatric (including restlessness, increased anxiety, nervousness), and other side effects for unexpected observations. Severity of each side effect was rated 0=absent, 1=mild, 2=significant and 3=discontinued medication because of the side effects.

Statistical analyses

As the normality assumption of the data was violated, comparisons of performance with/without MPH treatment were conducted with non-parametric Wilcoxon signed ranks tests in SPSS 26 (IBM). Results are corrected for multiple comparison using the Benjamini-Hochberg method (B-H; Thissen et al., 2002).

Results

Clinical symptomatology

At baseline, without MPH treatment, the sum of inattentive symptoms intensity was significantly higher than the sum of hyperactivity/impulsivity symptoms intensity (Mdn_{INATT}=23, Mdn_{HYPER}=12, Z=-3.926, p<.001, r=.62). After B-H correction (adjusted p=.015), sum of ADHD symptoms intensity significantly decreased with MPH treatment ($Mdn_{WITHOUT}$=34, Mdn_{WITH}=29, Z=-3.731, p<.001, r=.59). Reduction of symptom severity was observed both for the sum of inattentive symptoms ($Mdn_{WITHOUT}$=23, Mdn_{WITH}=18, Z=-3.733, p<.001, r=.59) and the sum of hyperactivity/impulsivity symptoms ($Mdn_{WITHOUT}$=12, Mdn_{WITH}=10, Z=-2.943, p=.003, r=.47). Comparing changes on single symptoms (see Figure 1), almost all inattentive symptoms decreased in intensity with MPH treatment, except for "loses things" symptom where change with MPH treatment was not significant (p=.317*).*

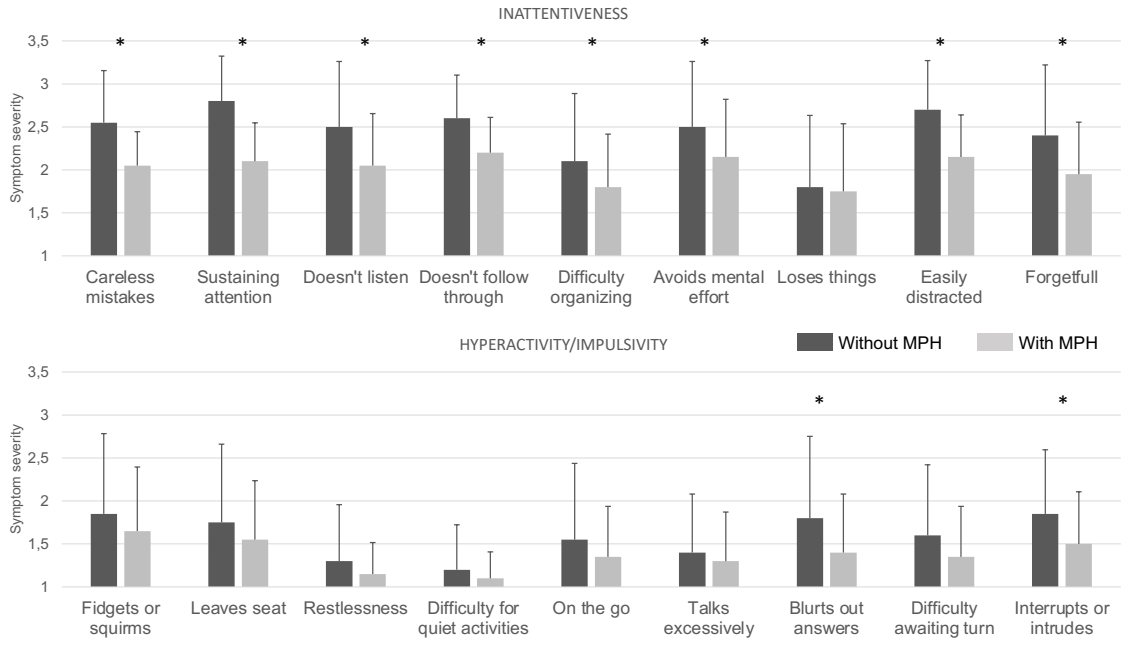

Figure 1: Severity of ADHD symptoms distributed by inattentive symptoms (top part) and hyperactivity/impulsivity symptoms (bottom part). Comparison surviving Benjamini-Hochberg correction are marked with a star.

For hyperactivity/impulsivity symptoms, again a majority of symptoms decreased significantly in intensity with MPH treatment. However, only "blurts out answers" and "interrupts or intrudes" survived the B-H correction (adjusted *p*=.015).

Cognitive measures

Attention

Without medication, mean group performance was in the clinical range (T-score ≥60) for measures of inattentiveness and impulsivity on the CPT task (see Figure 2). More specifically, elevated mean T-scores were observed for *Detectability* (mean=60; sd=7.24), *Perseverations* (mean=68.32; sd=13.73), *Hit Reaction Time Standard Deviation* (HRT SD; mean=66.86; sd=15.10) and *Variability* (mean=64.85; sd=11.39).

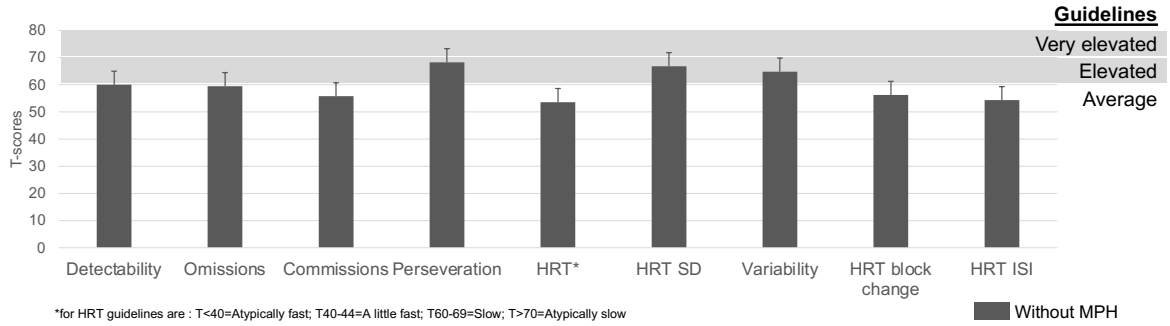

Figure 2: Standardized group performance (T-scores) on measures of attention from Conners' Continuous Performance Test 3rd edition. Scores in the grey area are considered to be within the clinical range.

As displayed in Table 3, after B-H correction (adjusted *p*=.007) a majority of measures of inattentiveness, impulsivity and vigilance significantly improved with medication. *Commissions errors* only showed a trend towards improvement (*p*=.051) and HRT SD did not survive the B-H correction (*p*=.039).

Looking closer at measures of sustained attention, a supplementary analysis block by block showed evidence for improvement of sustained attention with MPH (see supplementary material, Table S1).

Table 3: Comparison of attention, executive function, learning and long-term memory measures with/without MPH medication

Cognitive domain	Test name	Variable (raw scores)	Without MPH			With MPH			Wilcoxon signed rank test		Effect size	B-H correction
			Mean	SD	Median	Mean	SD	Median	*Z*	*p*	*r*	adjusted *p*
Attention	CPT-3	Detectability	-1,26	0,83	-1,39	-6,79	22,62	-2,00	-3,555	**<0,001**	0,54	0,005
		Omissions	7,82	9,86	3,00	3,14	4,94	1,00	-3,539	**<0,001**	0,53	0,004
		Commissions	55,41	15,37	54,50	48,32	18,68	43,50	-1,947	0,051	0,29	0,012
		Perseverations	3,18	3,26	2,00	1,64	1,76	1,00	-3,021	**0,003**	0,46	0,006
		Hit RT	448,74	127,44	406,50	395,75	101,51	361,84	-3,717	**<0,001**	0,56	0,003
		Hit RT SD	278,43	189,70	210,52	144,72	118,15	99,69	-4,107	**<0,001**	0,62	0,002
		Variability	132,30	98,89	103,17	62,37	64,41	33,24	-3,808	**<0,001**	0,57	0,002
		Hit RT block change	13,43	25,45	7,85	2,27	16,39	1,66	-2,062	0,039	0,31	0,011
		Hit RT ISI	49,30	54,23	27,30	19,21	28,55	16,85	-3,717	**<0,001**	0,56	0,001
Inhibition	Stroop	Inhibition ratio	0,49	0,22	0,50	0,58	0,19	0,59	-2,190	0,029	0,32	0,009
	Tower of London	Rule violation	2,36	3,03	1	0,73	1,55	0	-2,229	0,026	0,34	0,008
	Stop-Signal Task (CANTAB)	Stop-Signal RT	215,68	80,10	195,85	176,89	75,33	145,80	-2,938	**0,003**	0,43	0,005
Cognitive flexibility	Color Trail Test	Flexibility ratio	2,31	0,89	2,04	2,07	0,62	1,98	-0,365	0,715	0,05	0,022
	Intra-Extra-Dimensional (CANTAB)	EDS errors	20,04	9,952	23	15,04	12,279	13	-1,852	0,064	0,27	0,013
Updating	Digit span	Backward span	3,65	0,78	4	3,91	1,08	4	-1,054	0,292	0,16	0,018
	Letter-Number sequencing	Letter-Number span	4,57	0,90	5	4,70	1,02	5	-0,832	0,405	0,12	0,019
	Spatial Working Memory (CANTAB)	Between Errors (4 Boxes)	0,49	0,66	0,25	0,48	0,71	0,25	-0,095	0,925	0,01	0,025
		Between Errors (6 Boxes)	3,57	1,69	3,5	3,38	1,64	3,5	-0,309	0,757	0,05	0,023
		Between Errors (8 Boxes)	7,47	2,91	8	7,45	2,97	7,25	-0,318	0,751	0,05	0,023
Initiation	Verbal fluency	Number of animals produced	15,61	4,387	16	15,41	3,875	15	-0,525	0,600	0,08	15,61
	Non-verbal fluency	Different items produced	23,35	9,64	22	25,87	11,66	24	-1,864	0,062	0,27	0,013
Planning	Tower of London	Total moves	38,68	15,09	37	41,23	19,79	39,5	-0,504	0,614	0,08	0,020
Processing speed	Coding	Number of codes produced	42,57	16,72	40	48,17	16,96	52	-2,696	**0,007**	0,40	0,007
	Symbol Search	Number of symbols identified	22,22	8,32	22	25,00	8,52	26	-1,811	0,070	0,27	0,014
Learning	15 signs	learning score signs	2,18	1,24	1,83	2,64	1,37	2,33	-2,156	0,031	0,32	0,010
	15 words	learning score words	3,60	1,74	3,25	3,42	1,82	3	-0,466	0,642	0,07	0,021
Long-term memory	15 signs	Retention % thirty minutes	96,45	14,12	100,00	92,14	10,34	91,67	-1,503	0,133	0,22	0,015
		Retention % on day	68,17	19,68	66,67	62,33	21,28	66,67	-1,067	0,286	0,16	0,017
		Retention % on week	57,87	22,68	60,00	51,77	23,52	57,14	-1,12	0,263	0,17	0,016
	15 words	Retention % thirty minutes	77,70	16,75	78,57	91,26	12,90	91,67	-2,207	0,027	0,33	0,009
		Retention % on day	62,85	21,94	66,67	70,80	20,52	73,08	-0,224	0,823	0,03	0,024
		Retention % on week	49,11	26,25	50,00	57,19	24,00	61,54	-1,429	0,153	0,21	0,016

NB: RT = Reaction Time; SD = Standard Deviation; ISI= Inter-Stimulus Interval; EDS = Extra-Dimensional Shift
Significant p-values after Benjamini-Hochberg (B-H) correction are displayed in **bold**

Indeed, there was a significant decrease in *HRT* with MPH at the end of the task, for block 5 ($Mdn_{WITHOUT}$=424, Mdn_{WITH}=389.5, Z=-4.107, p<.001, r=.62) and block 6 ($Mdn_{WITHOUT}$=441.5, Mdn_{WITH}=368.5, Z=-3.100, p=.002, r=.47). HRT SD was significantly lower in all the blocks (ps<.008) with medication. Finally, *Omission errors* were significantly lower with MPH medication in the second half of the task, for block 4 ($Mdn_{WITHOUT}$=4, Mdn_{WITH}=1, Z=-2.462, p=.014, r=.37) and block 6 ($Mdn_{WITHOUT}$=8, Mdn_{WITH}=1, Z=-3.430, p=.001, r=.52). Comparisons reported here survived the B-H correction (adjusted p=0.025).

Executive functions

As displayed in Table 3, significant improvement of performance with MPH was only visible on measures of inhibition and one measure of processing speed (Coding). However, only *Stop-Signal Reaction Time* ($Mdn_{WITHOUT}$=195.85, Mdn_{WITH}=145.80, Z=-2.462, p=.003, r=.43) and *Coding* ($Mdn_{WITHOUT}$=40, Mdn_{WITH}=52, Z=-2.696, p=.007, r=.40) survived the B-H correction for multiple comparisons (p<.008). No other comparison of cognitive flexibility, updating, verbal and non-verbal initiation or planning reached statistical significance.

Learning and long-term memory

No significant improvement with MPH was found for acquisition or retention of information over time in verbal or non-verbal modalities (see Table 3).

Daily-life observations

As shown in Table 4, without medication, caregivers reported clinically significant executive dysfunctions in daily-life using the BRIEF questionnaire (mean T-scores for GEC, BRI and MI ≥65). More specifically, domains of inhibition, flexibility, emotional control, initiation, working memory and planning were reported as problematic.

With medication, only the emotional control subscale showed significant improvement ($Mdn_{WITHOUT}$=65, Mdn_{WITH}=60, Z=-2.162, p=.031, r=.03). However, this result did not survive the B-H correction (adjusted p=.002).

Table 4: Comparison of daily-life behavior with/without MPH medication

		Without MPH			With MPH			Wilcoxon signed rank test		Effect size	B-H correction
	Variable (T-scores)	Mean	SD	Median	Mean	SD	Median	*Z*	*p*	*r*	adjusted *p*
BRIEF	Inhibition	65,17	17,58	66	63,48	16,44	59	-0,589	0,556	0,56	0,020
	Shifting	71,83	15,44	72	67,52	15,04	68	-1,532	0,126	0,13	0,007
	Emotional control	65,17	18,36	65	60,13	15,13	60	-2,162	0,031	0,03	0,002
	Bahvioral Regulation Index (BRI)	69,96	17,46	69	65,87	15,02	64	-1,812	0,070	0,07	0,005
	Initiation	68,26	13,60	72	67,00	14,64	66	-0,244	0,807	0,81	0,025
	Working memory	71,52	10,49	73	66,83	12,71	69	-1,512	0,131	0,13	0,009
	Planning	67,70	11,40	66	66,26	13,02	67	-0,767	0,443	0,44	0,018
	Organisation	59,74	12,48	62	57,48	10,88	57	-1,428	0,153	0,15	0,011
	Monitoring	64,35	12,63	66	64,39	12,52	62	-0,281	0,779	0,78	0,023
	Metacognitive Index (MI)	69,87	10,82	73	66,96	11,82	68	-1,035	0,301	0,30	0,016
	Global Executive Composite (GEC)	71,22	12,71	73	68,30	12,98	70	-1,309	0,191	0,19	0,014

Significant p-values after Benjamini-Hochberg (B-H) correction are displayed in **bold**

In a complementary qualitative analysis based on 5 participants who completed the BRIEF self-report, without medication, participants reported no problems in any of the daily-life EF examined (mean T-score <65). Change with medication could not be assessed because of insufficient sample size.

Safety and tolerance to treatment

Changes in QTc values did not exceed the cut-off of 30 milliseconds on the electrocardiogram done on Day six after beginning of treatment.

A large majority of naïve participants (15/16) reported at least one side effect during the study. However, treatment was never discontinued due to adverse side effects. Following the first MPH dose at Day one, 9 participants (56.25%) reported some side effect. After increasing the dosage at Day six, 13 participants (81.25%) reported some side effect. At the end of the treatment phase on Day thirteen, 11 participants (68.75%) reported some side effect. As displayed in Table 5, gastro-intestinal and sleep disturbances were mostly represented. More specifically, a qualitative analysis showed that decreased appetite and difficulties falling asleep were the most common side effects reported.

Table 5: Frequency and intensity of side effects at Day 1, 6 and 13 of methylphenidate treatment

	Mild N (%)			Significant N (%)			Total N (%)		
Side effect category	Day 1	Day 6	Day 13	Day 1	Day 6	Day 13	Day 1	Day 6	Day 13
Gastro-intestinal	5 (55.56)	11 (84.62)	6 (54.55)	0	0	0	5 (55.56)	11 (84.62)	6 (54.55)
Sleep disturbances	3 (3.33)	5 (38.46)	7 (63.64)	2 (22.22)	2 (15.38)	2 (18.18)	5 (55.56)	7 (53.85)	9 (81.82)
Neurologic	0	0	2 (18.18)	0	0	0	0	0	2 (18.18)
Cardio-vascular	0	1 (7.69)	0	0	0	0	0	1 (7.69)	0
Mood	0	0	1 (9.09)	0	0	1 (9.09)	0	0	2 (18.18)
Other psychiatric	0	0	1 (9.09)	2 (22.22)	2 (15.38)	0	2 (22.22)	2 (15.38)	1 (9.09)
Other	0	0	0	1 (11.11)	0	0	1 (11.11)	0	0

Gastro-intestinal side effects tended to be more frequent after dosage increase (84.62%) but slightly less frequent at the end of the treatment phase (54.55%). On the contrary, frequency of sleep disturbances tended to increase from the beginning of treatment (first dose=44.44%; dosage increase=53.85%) and were most frequent at the end of the treatment phase (81.81%). Regarding intensity, the majority of reported side effects were mild, significant sleep disturbances were reported across all stages of treatment.

Discussion

The general aim of this study was to bring additional knowledge on the possible effects of a stimulant medication (methylphenidate) in patients with 22q11DS. To fully grasp the observed changes, the outcome was measured at different levels (core ADHD symptoms, cognitive measures and daily-life behavior). Finally, tolerance to treatment was investigated in a sub-group of patients naïve to the molecule.

First of all, our results showed a significant diminution of core ADHD symptoms (reported by the parents) with medication. These results replicate findings from idiopathic ADHD and extend specific findings from the 22q11DS population (Cortese et al., 2018; Gothelf et al., 2003; Green et al., 2011). Improvement was shown for both symptoms of inattentiveness and hyperactivity/impulsivity although the later were on average significantly less severe in our

sample. This observation is coherent with the predominant inattentive type consistently found in 22q11DS (Niarchou et al., 2015). On the symptom level, not surprisingly, symptoms with highest ratings without MPH, like “sustaining attention” or “easily distracted” were the ones that improved the most with medication. While less frequent symptoms or symptoms staying in the subclinical range, like “losses things”, “fidgets or squirms” or “leaves seat”, showed no significant change.

Secondly, regarding cognitive measures, a wide range of domains were assessed. However, in this sample, we observed a selectivity in the effects of MPH with only measures of attention and inhibition robustly improving with medication. Some measures of processing speed also significantly improved but could also be tainted by a learning effect on that specific task (Coding) and would need to be confirmed with other measures. Regarding attention, we replicated previous findings of a significant decrease of measures of inattentiveness with MPH (Gothelf et al., 2003). By including more indicators in our analyses, we extend findings to measures of sustained attention and vigilance which also improved with medication. Overall, with MPH, participants were able to stay more attentive to the task and for longer delays with less fluctuation of attention. When it comes to EF, improvement of prefrontal cognitive functioning with MPH has previously been demonstrated in 22q11DS, however selectivity of different subdomains improving was difficult to disentangle (Green et al., 2011). Nonetheless, the authors showed that performance on the cognitive task only taxing working memory was not affected by MPH, while tasks taxing both working memory and inhibition improved significantly with medication, which hints to a certain selectivity. Our findings confirm that mostly inhibition and not all EF are improved with medication in 22q11DS. This is in contrast with findings from idiopathic ADHD where performance on multiple EF domains are reported to be ameliorated with MPH (Coghill et al., 2014; Nigg, 2005). One explanation could come from the higher dosage of MPH used (individual dose from 18-90mg in Coghill et al., 2014) or

even the use of titration to find the optimal clinical response before evaluating effects on cognition (e.g., Yang et al., 2012). Another important point to consider is that EF deficit is part of the 22q11DS neuropsychological profile, independently of low intellectual functioning and ADHD comorbidity (Maeder et al., 2016; Moberg et al., 2018; Shapiro et al., 2014). This suggests that poor performance on EF in 22q11DS is not necessarily related to ADHD symptomatology and therefore might not respond as well to ADHD medication. In the same way for long-term memory, no previous study has investigated the effect of MPH in 22q11DS, although in idiopathic ADHD results from a review and meta-analysis showed that effects of MPH are significantly superior to a placebo (Coghill et al., 2014). Nonetheless, deficits in non-verbal learning and both verbal and non-verbal memory retention over time have been demonstrated independently of ADHD comorbidity in 22q11DS (Lajiness-O'Neill et al., 2005; Lepach & Petermann, 2011; Maeder et al., 2020). This suggests that mechanisms leading to inefficient learning and memory retention are different to those observed in the context of idiopathic ADHD and therefore are not as sensitive to MPH medication. To summarize, the results of the present study show a selective improvement of inhibition while other cognitive domains stayed relatively unchanged with medication.

Thirdly, daily-life behavior was assessed by the parents with a specific focus on executive dysfunction with the BRIEF questionnaire, providing an ecological assessment tool. Although participants displayed executive dysfunction on several subscales including inhibition, flexibility, emotional control, initiation, working memory and planning, no significant change was reported with medication. This is in contrast with finding from idiopathic ADHD, where improvement of daily-life EF with stimulants (including slow-release MPH) has been shown using the BRIEF questionnaire (Taş Torun, Işik Taner, Güney, & İseri, 2020; Turgay et al., 2010; Yang et al., 2012). Again, higher dosage and dosage optimization should be considered in the interpretation of this comparison. Additionally, in our situation, as a majority of

participants were naïve to MPH and were only medicated for a short period (13 days), lack of results could come from insufficient observations possibilities. Unfortunately, our sample of consumer participant (N=7) was too small to run any comparison. Future studies should consider longer treatment periods when this type of questionnaire is used or use it with more chronic MPH users.

Results from the qualitative additional analysis on self-reported executive dysfunction in daily-life revealed that while caregivers reported important impairments in several domains, young adults did not identify any difficulties. While coming from a limited sample, this observation suggests that young adults with 22q11DS experience difficulties in assessing their own strength and weaknesses. This observation is in line with previous results comparing patient and parent answer on the BRIEF questionnaire (Taylor, Kates, Fremont, & Antshel, 2018). The authors found evidence that young adults with 22q11DS do not perceive themselves as experiencing difficulties in every-day life. Additional research is needed to confirm our preliminary findings and explore if difficulty to assess one's own behaviors is restricted to executive dysfunction (possibly coming from a type of anosognosia) or if it is a more general phenomenon for all types of self-assessment (related to the low intellectual functioning which characterizes this population).

Finally, safety and tolerance to MPH medication was assessed in the naïve group replicating previous findings in 22q11DS (Gothelf et al., 2003; Green et al., 2011). Although a higher dosage/kilo was used with respect to prior studies (0.7mg/kg instead of 0.3mg/kg or 0.5mg/kg), treatment was well tolerated with no change in cardiac measures and no adverse effect resulting in interruption of treatment. Similarly, to both previous studies, side effects were present in a majority of participants, but mostly of mild intensity. The most common side effects reported were form the gastro-intestinal category and sleep disturbances, matching general observations from idiopathic ADHD (Banaschewski et al., 2006). Interestingly, in this study, higher rates of

sleep disturbances were reported. Indeed, while sleep disturbances are a common side effect of MPH, no side effects related to trouble sleeping were reported in the study from Gothelf et al. (2003). The absence of insomnia was explained by the fact that the medication was given once in the morning at a very low dosage. As for Green's study (2011), trouble sleeping was present in almost half of the participants and tended to be persistent after 6-month follow-up. However, the dosage was still quite low and could explain some difference with the findings from our study. It is worth mentioning also that sleep disturbances in 22q11DS are very frequent (60%) and not only related to the presence of ADHD (Moulding et al., 2020).

Limitations

Findings from this study are limited by the sample size (N=23) and the broad age-range (children to early adulthood) included here. Indeed, as a rare genetic condition, prevalence of 22q11DS is approximatively 1:4000 live births (Botto et al., 2003). Furthermore, the high comorbidity of psychiatric conditions reported in this syndrome, particularly psychosis spectrum disorder, creates difficulties in finding suitable participants for a clinical trial with stimulants (Rees et al., 2014; Schneider, Debbané, et al., 2014). Interestingly, naïve participants were much easier to find compared to participants who already have a prescription of MPH. One possible explanation is a recruitment bias caused by satisfaction with MPH treatment. Indeed, 22q11DS patients with treatment are possibly satisfied with their currant care and do not seek additional help through clinics or clinical research projects, while participants from the naïve group did.

Related to the small sample, no formal ADHD diagnosis was required for inclusion in the study, only attention difficulties pointed out by parents and/or the participant. However, all participants presented with at least ADHD traits and confounding origins of attentions difficulties (e.g., insomnia, psychosis spectrum disorder) were ruled out by a trained psychiatrist (SE) prior to inclusion in the study.

Another shortcoming from this design is the short treatment phase in the naïve group. Originally, a short period of time was chosen to maximize participation to the study. However, treatment duration was often insufficient for patients and caregivers to really appreciate change. It also prevented further increase and adaptation of the dosage for each participant which could have led to different results. Related to the issue of treatment optimization, the fixed dosage depending on weight prevented a more individual approach, as response to treatment varies significantly between individuals (Huss et al., 2017). Future studies should consider introducing dosage titration to optimize response to treatment. Indeed, because of gastrointestinal problems affecting 30% of individuals with 22q11DS (e.g., McDonald-McGinn et al., 2015), blood dosage could be even more variable.

A final limitation from this study is the lack of information from school/work environment. Indeed, contrary to the majority of studies in idiopathic ADHD and the studies on 22q11DS, only parents were asked to assess change with medication. Because of fear of stigmatization, some parents chose not to share the specific diagnosis outside the family environment. Additionally, some young adults were between occupation during the study. For these reasons, third party observations were not included.

Clinical implications

Results from this study provides important information for clinicians and caregivers involved in management and care of individuals with 22q11DS. First of all, safety and tolerance to treatment were replicated in an independent sample providing additional evidence for using MPH in this genetic condition. Secondly, MPH was found to significantly reduce the core ADHD symptoms reported by the parents as well as improving attention and inhibition measures. Finally, results from the self-report questionnaire highlighted difficulties for young adults with 22q11DS to identify their limits. This suggest that multiple informants are required to get a representative overview of an individual's functioning.

Conclusions

In sum, this study shows effectiveness of a short treatment of MPH in 22q11DS patients. Benefit from the treatment was demonstrated by diminished core ADHD symptoms, specifically inattention symptoms, and improvement of cognitive measures. Results showed a selectivity of improvement on cognitive measures, with attention and inhibition being robustly ameliorated by MPH while other measures of EF, learning and memory were not. Conversely, no significant improvement on ecological measures of daily-life EF was found, possibly because of the short treatment period.

Ethics approval and consent to participate

The study was approved by the Ethical Committee of the Canton of Geneva (CCER, Switzerland) as well as the Swiss Agency for Therapeutic Products: Swissmedic. Project number: PB_2016-01472. The trial is registered at: ClinicalTrials.gov, ID: NCT04647500, https://www.clinicaltrials.gov

Written informed consent was obtained for all participants and their parents (if participant were younger than 18 years).

III. DISCUSSION

With this thesis we centered our research around the cognitive impairments observed in the 22q11DS population. The first objective was to specify and extend knowledge on the neuropsychological profile of 22q11DS, with a focus on EF and attention, as well as memory. We investigated developmental trajectories of EF and created new tools to measure memory retention and forgetting. The second objective was to move past the description of observed deficits or atypical developmental pattern to evaluate a type of intervention by examining the effect of medication on the cognitive processes described previously. We provided evidence for the benefit of MPH on ADHD symptoms and cognitive measures.

1. Main findings from empirical studies

1.1. Study 1

In the first study, the main goal was to examine developmental patterns of EF between 6 to 26 years old in 22q11DS, compared to healthy controls. Trajectories of multiple sub-domains of EF were investigated separately, including working memory, inhibition and verbal initiation (verbal fluency). Analyses were performed on a longitudinal dataset composed of 352 assessments from 195 participants (95 with 22q11DS), ranging from one to four assessments per participants.

Overall, lower performance in the 22q11DS group was observed in all the sub-domains examined. However, only working memory and verbal fluency displayed deviant developmental patterns from the control group, while measures of inhibition followed a similar pace of development. More specifically for working memory, the 22q11DS group displayed minimal improvement with age characterized by performance reaching a developmental plateau much faster than controls. Similarly, for verbal fluency, while scores were comparable between groups at a younger age (6 to 8 years), they failed to improve with age in the 22q11DS group,

lagging behind the typically developing individuals. Results remained unchanged when only patients with 22q11DS and a full-scale IQ higher than 70 were compared to controls. This provides additional evidence that the group difference reflects specific impairment in EF domains and is not a by-product of intellectual ability.

Relationship between atypical developmental trajectories with age and symptoms of psychosis, measures with the Positive and Negative Syndrome Scale, PANSS (Kay et al., 1967) was examined within the 22q11DS group. By comparing trajectories of patients who displayed psychotic symptoms at any assessment to those who did not, a link between certain executive domains and negative symptoms (e.g., anhedonia, avolition, emotional blunting) was found. Indeed, improvement of performance with age was minimal for measures of inhibition and working memory in individuals showing negative symptoms. Results provide additional evidence for an association of EF and negative symptoms of psychosis and suggest EF impairment can be visible before the onset of symptoms.

1.2. Study 2

The second study builds on results from the first one and continues to deepen the knowledge on developmental trajectories of EF in 22q11DS. In a slightly wider age range (8 to 35 years old) with a dataset composed of longitudinal assessments (one or two assessments per individual) the study confirms and extends previous findings. By using a wider range of EF and attention sub-domains with multiple tasks per domain, results provide a more in depth understanding of the developmental pattern observed (developmental deficit, lag, deterioration or maturation) for each cognitive sub-domain.

This work brings two major highlights to the current literature. First of all, in the examined age window, a majority of variables investigated showed improvement with age in both groups and no evidence for cognitive decline was found. Domains not improving stayed stable with age suggesting the age window does not contain the period of greatest change. Compared to healthy

controls, 22q11DS performance showed patterns of developmental deficits (i.e., lower levels of performance but regular improvement) and developmental lags (i.e., improvement at a slower pace with age). However, neither developmental maturation (i.e., initial cognitive impairment but development catches up with the control group) nor deterioration (i.e., decline in absolute ability) were observed.

Secondly, the cognitive domains examined yielded different patterns of development confirming de diversity of EF in patients with 22q11DS. Furthermore, when examined with multiple tasks, only two domains (inhibition and initiation) yielded one consistent developmental pattern on all tasks, while the other three (flexibility, updating and focal attention) yielded different developmental models, depending on the task. These results bring to light the complexity of EF and attention with the necessity to consider performance depending on sub-domain, task, modality of testing (verbal vs non-verbal) or outcome measure (speed vs. accuracy).

1.3. Study 3

In the third study, focus shifted to another feature of the 22q11DS cognitive phenotype: memory. More specifically, long-term memory and forgetting. Based on reports of families of 22q11DS patients, an episodic memory task was created to explore memory retention over longer delays in time, up to one month. Eighty-four participants (45 with 22q11DS), aged 8 to 24 years, completed the task. By adding additional retrievals than standardized memory tools used in a clinical setting or for research, trajectory of forgetting was examined. As mentioned previously, to bypass deficient learning processes with visual stimuli and focus on memory retention, only the verbal part of the task is considered.

With this design, evidence for accelerated rates of forgetting in the 22q11DS population was shown. Indeed, while learning and retention performance after a delay of thirty minutes were comparable between 22q11DS and healthy controls a significant difference in performance

appeared after a delay of one day. Thereafter, it continued to decrease faster in the 22q11DS with time, widening the difference with the control group after each delay (one week and one month). Similar findings are found for recognition performance, with a steeper loss in the 22q11DS group with time (different trajectories of forgetting). However, result show fewer items correctly recognized in the 22q11DS group compared to controls already after a delay of thirty minutes indicating overall weaker recognition processes in 22q11DS.

Looking at the heterogeneity of performance in the 22q11DS group, a cluster analysis was performed on retention scores to identify subgroups of patients. Two different approaches were done, the first one with raw scores and the second one with scores corrected for learning performance. The first approach identified two subgroups, one with memory retention performance and similar trajectory to the control group et the second one with a much steeper decline over time. It was suggested that the second group is possibly driving the overall accelerated forgetting rate observed in 22q11DS compared to healthy controls. Contrasting profiles of the subgroups yielded by the cluster analysis, results showed that the group with lower memory retention had significantly lower full-scale IQ and higher rates of positive psychotic symptoms (e.g., delusions, suspiciousness, hallucinations), measured with the Structured Interview for Prodromal Syndromes (SIPS), Positive And Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) (Kay et al., 1967; Miller et al., 2004; Overall & Gorham, 1962). There was no difference in age between both subgroups. In the second clustering approach, scores of memory retention were corrected for learning performance by calculating a percentage of retention based on the number of words remembered at the end of the learning phase. This technique allowed to isolate only memory retention, independently of learning processes. Again, in the 22q11DS population two subgroups were identified one large group with memory performance resembling the control population and one subgroup with a significantly different trajectory of retention over time.

With this cluster solution, the subgroup with lower performance in memory retention showed impairment already after a delay of thirty minutes. This suggested that for this subgroup, although learning was controlled for, retrieval of memory is impaired already after delays of thirty minutes. Description of the profile of this subgroup with lower memory performance, yielded no difference in age (compared to the 22q11DS higher memory performance) but significantly lower full-scale IQ and a trend to higher disorganization symptoms of psychosis.

In the last part of this third study, neuronal correlates of verbal memory retention performance were examined by comparing hippocampal volume between subgroups within the 22q11DS population. Interestingly, no difference was found between groups with the clustering technique based on raw memory retention scores. However, significantly lower hippocampal volume was found in the subgroups with lower performance, in the clustering technique based on memory scores corrected for learning performance. This suggests that hippocampal alterations may specifically affect memory retention in 22q11DS patients.

1.4. Study 4

The fourth study extends findings from Study 3 on faster forgetting in 22q11DS and brings further knowledge on memory retrieval processes over long delays. Compared to the previous results it examines whether increased forgetting in patients compared to controls reflected deficits in retrieval of memories acquired remotely (long delays) or if this population is more susceptible to interference during memory reconsolidation occurring at each recall. Therefore, this study examined retention in verbal and non-verbal memory over a one-month delay, with and without potential interference through reconsolidation.

Although limited by a small sample size (N=48), the results from the new design (partial design) replicate and extend the previous findings. While performance on retrieval did not differ after

thirty minutes, reduced rates of retrieval were found in the 22q11DS group after one month in both verbal and non-verbal modalities, compared to controls.

Comparing the designs (partial design vs full design) provided insight on the benefits of reconsolidation processes. Indeed, both patients and control participants retrieved significantly more information after a delay of one month with the presence of recalls at one day and one week. For this reason, it was suggested that the intermediate recalls helped stabilizing the memory trace rather than weakening it, in all the participants.

Finally, analysis of error rates showed no difference between patients and controls adding evidence for faster forgetting due to a decay of the memory trace, rather than an interference.

1.5. Study 5

The last study presented here contains the results form a clinical trial evaluating the safety and effectiveness of MPH in 22q11DS. Outcome was evaluated on core ADHD symptoms, cognitive measures of attention, EF and memory, as well as questionnaires reflecting daily-life functioning in a sample of 23 individuals with 22q11DS. The principal aim of this study was to extend the range of cognitive measures examined, compared to previous studies.

Altogether, the MPH treatment was found to benefit the participants of the study. In addition to improvement of core symptoms of ADHD (specifically inattentive symptoms), findings showed a selectivity of the effects, with improvement noted only for cognitive measures of attention, and inhibition, while other cognitive domains stayed relatively unchanged with medication. Conversely, no significant improvement on ecological measures of daily-life executive functioning was found, possibly because of the short treatment period.

As a second aim, confirmation of safety and tolerance to treatment was found in a subgroup of 16 participants naïve to the molecule over a trial of 13 days of MPH treatment. This is of particular interest since hereby findings from previous studies were replicated in an independent sample, strengthening current knowledge to guide clinicians. More specifically, although side

effects of MPH were very frequent, their nature was consistent with observations form idiopathic ADHD as well as 22q11DS and their intensity was mostly mild.

1.6. Conclusions from the empirical studies

From the findings reported in the five studies, we are now able to answer several of the open questions from the literature. First of all, both studies 1 and 2 highlighted that although performance on a majority of sub-domains of EF are significantly lower in 22q11DS (compared to controls) some domains tend to be more affected than others. For example, measures of initiation and working memory tended to show developmental lag, suggesting the deficits will only become more important with time. Conversely measures of inhibition or cognitive flexibility showed either developmental deficits indicating lower performance but still improving at the same rates as expected for the health controls trajectories, and some in some measures no deficit at all. Results provided insight into different indicators possibly influencing results (accuracy vs. speed).

For studies 3 and 4 tackling memory retention, results showed the limits of the current standardized tools available and the necessity to develop new and adapted ones for investigating forgetting over longer delays of time. Indeed, trajectories of memory retention showed significantly steeper forgetting with less information recalled in the 22q11DS already after one day. Furthermore, evidence suggests that participants with 22q11DS struggle with recalling memories, particularly remotely acquired memories, and that multiple recalls over time slows forgetting down in both 22q11DS and controls.

Finally, study 5 showed that MPH is a valuable option to consider in 22q11DS since the medication is relatively well tolerated and improves both core clinical symptoms of ADHD as well as cognitive measures of attention and inhibition.

2. Clinical implications

In light of the empirical findings presented in this work, several clinical implications emerge. These are relevant for patients, caregivers and clinical practicians, providing additional information to elaborate recommendations for management and care of these patients. They are also relevant for the development and validation of intervention programs using cognitive training or medication.

2.1. Neuropsychological profile and assessment

The results allow an update and the expansion of the neuropsychological profile of patients with 22q11DS, particularly on the topic of memory. In Studies 3 and 4, by investigating memory retention on long delays, faster forgetting rates of both verbal and non-verbal memory (after controlling for learning performance) was identified, challenging the view of relatively unimpaired verbal memory. Moreover, updating the neuropsychological profile, brings the necessity to systematically investigate memory retention over long delays when dealing with 22q11DS patients with adapted tools or via interview to identify potential impairment.

As for EF, the comparison of developmental trajectories of multiple cognitive sub-domains with several task in Study 2 highlights the fact that tools chosen for assessment can reflect a partial view of the profile. Indeed, multiple indicators, covering different modalities of testing are necessary. In line with this, the qualitative analysis of a self-reported questionnaire in Study 5 suggests that young adult with 22q11DS have difficulties to identify their own strengths and weaknesses (at least for the EF domains evaluated). This observation calls for the need of multiple informants (e.g., parents, teacher, employer) in the context of assessments for a global view on cognitive functioning.

Finally, findings on developmental trajectories in Studies 1 and 2, adds to previous literature demonstrating that the cognitive profile is not static over time (Swillen, 2016; Swillen & McDonald-McGinn, 2015; Vorstman et al., 2015). This observation warrants the need

for periodic comprehensive neuropsychological assessments with 22q11DS patients to identify strength and weaknesses and adjust or re-adapt the demand to the situation.

To sum up, guidelines for care and management of 22q11DS patients should include a comprehensive neuropsychological assessment tackling a wide range of domains with multiple tasks per domains to identify strength and weaknesses in the profile. Due to the atypical developmental patterns highlighted here, ideally neuropsychological assessment should be repeated regularly following scholar key milestones. Furthermore, reassessing skills in late adolescence or early adulthood could provide important information for transition into the professional world.

2.2. Intervention

Results from both Study 1 and 2 identified divergent paths of development at a relatively early age. Therefore, cognitive and educational interventions should be implemented as early in childhood as possible to prevent or slow down future impairments. More specifically, for EF, in Study 1 and 2, delineating atypical developmental trajectories allows to determine the most suitable intervention strategy to implement. For example, in the context of developmental deficit, compensatory strategies could be implemented depending on identified strength in the cognitive profile. Alternatively, domains showing developmental lag should receive increased attention early on and could be interesting targets for cognitive training. For memory, Study 3 highlights the need for implementing memory aids to compensate or to slow down forgetting over time. Additionally, Study 4 showed a similar benefit of multiple recalls over time, suggesting that regular reminders or repetitions of previously learned information can benefit individuals with 22q11DS.

In the current literature, only a handful of studies have validated cognitive training programs tailored specifically to the need of 22q11DS patients or individuals with a lower intellectual functioning. Until now, they particularly focused on attention and EF, visuo-spatial skills and

social cognition (Demily et al., 2016; Glaser et al., 2012; Harrell et al., 2013; Mariano, Tang, Kurtz, & Kates, 2015). Although demonstrating promising results, no measurement of transfer to daily life and the absence of follow-up evaluations after the end of the intervention limits the scope of the results obtained. One study examined the durability of the improvement with a six month follow-up and encouragingly found that the gains reported at the end of the intervention program remained stable (Mariano, Tang, Kurtz, & Kates, 2018). With regards to memory, recommendations for children and adolescent with 22q11DS in the classroom include additional opportunities for repetition of the topics previously learned and the need for teaching memorization techniques (Reilly & Stedman, 2013). However, it remains to be further examined if a program targeting strategies for enhanced information acquisition and/or strengthen memory retention can be meaningful for patients with 22q11DS.

Finally, the results of the clinical trial with MPH from Study 5 add information on safety and effectiveness of this type of medication in the context of a genetic condition such as 22q11DS. Of particular interest, findings on cognitive measures suggest a selectivity of this medication on domains of attention and inhibition, rather than a global improvement. Conversely, core symptoms of inattention were more generally improved. Future work should consider examining the effects of cognitive training together with medication.

3. Contributions and perspectives

A number of topics only briefly covered in the studies presented here could provide interesting targets for future work. The following sub-sections develops a selection of relevant perspectives to consider.

2.1. Atypical brain development and cognition

In the introduction we briefly reviewed the neuroimaging findings of the 22q11DS literature, pointing towards atypical brain development in this population. In the context of this work, the

findings from atypical developmental of the frontal regions and reduced hippocampal volume are of great interest.

Two independent studies have provided evidence for excessive cortical thinning of frontal regions during adolescence in 22q11DS (Ramanathan et al., 2017; Schaer et al., 2009). Results from Study 1 and 2 provide indirect evidence that altered brain maturational process results in atypical developmental patterns of EF and attention processes in 22q11DS. However, using a combination of fMRI with a specific task targeting EF and/or attention could highlight more fine-tuned differences. For example, studies targeting working memory have shown significant differences in brain activation during an fMRI task (patients vs. controls), while behavioral results were comparable between groups (Harrell et al., 2017; Montojo et al., 2014). Future work should focus on linking neuroimaging and behavioral results in order to get a more fine-grained understanding of the developmental mechanisms and their underlying neural pathways. Regarding hippocampus, volume reduction in subfields has been found in patients across the psychosis spectrum (Nakahara, Matsumoto, & van Erp, 2018; Vargas et al., 2018). The same results are consistently observed in 22q11DS (Debbané et al., 2006; DeBoer et al., 2007; Kates et al., 2006; Mancini et al., 2019; Scott et al., 2016). In Study 3, a subgroup of individuals with 22q11DS exhibiting lower memory retention also had lower hippocampal volume. Furthermore, disrupted long-range synchrony between the hippocampus and prefrontal cortex (PFC) has been demonstrated in a mouse-model of 22q11DS (Sigurdsson et al., 2010). In this line, results from Study 4 pointing towards impaired retention of distant memories indirectly suggest a form of disruption between hippocampus and PFC, which roles are complementary in memory processing and necessary during retrieval of remotely acquired memories (Eichenbaum, 2017; Euston et al., 2012; Preston & Eichenbaum, 2013). To our knowledge, recall of memories acquired remotely have not yet been investigated with neuroimaging

techniques giving access to the functional connections underlying impaired behavioral performance.

2.2. Relationship between cognition and psychosis

Due to the increased risk for developing psychotic symptoms or schizophrenia spectrum disorder, 22q11DS provides a rare opportunity to investigate the relationship between cognition and psychosis (Rees et al., 2014; Schneider, Debbané, et al., 2014). Indeed, the current literature considers schizophrenia as a neurodevelopmental disorder where early abnormal brain development leads to cognitive deficit which precedes the onset of psychosis (Bora & Murray, 2014; Insel, 2010; Jahshan et al., 2010; Reichenberg et al., 2010). Studying the characteristics of the neurocognitive profile of individuals at genetic risk for psychosis potentially provides insight regarding preclinical stages of psychosis and future outcome. Following this idea, work from an international consortium investigated intellectual functioning in relationship to psychosis in a large sample of 411 individuals with 22q11DS (Vorstman et al., 2015). The authors showed that participants who developed a psychotic illness displayed a steeper decline of verbal IQ over time, making cognitive decline a robust indicator of the risk of developing a psychotic disorder.

Looking at more specific cognitive abilities than full-scale IQ or verbal and performance IQs, both memory and EF impairment are considered landmarks of the cognitive profile of schizophrenia (Fioravanti et al., 2012) and therefore targets of this work. In 22q11DS literature, two large studies have compared cognitive performance of adults with or without a psychotic disorder (Fiksinski et al., 2019; Weinberger et al., 2016). In both studies, results indicated lower performance of verbal and visual memory for 22q11DS patients with a psychotic disorder. This indicates that memory impairment should be considered a valuable indicator of the onset of psychosis, yet to our knowledge, no studies have investigated the trajectories of memory functioning in a longitudinal design (following individuals from childhood to early adulthood).

Conversely for EF, results are more inconsistent. Weinberger et al. (2016) found significantly worse performance on an EF composite score (composed of tests of abstraction and mental-flexibility, attention and working-memory) measured with the computerized Penn Computerized Neurocognitive Battery in 22q11DS participants with a psychotic disorder. In the study from Fiksinski et al. (2019) all participants displayed impairment in the "Executive Performance" domain (composed of tests of inhibition, cognitive flexibility, visual processing, drawing and immediate recall of shapes) regardless of whether or not they suffered from a psychotic illness. The authors suggest that "Executive Performance" may be a core expression of the underlying genetic risk of schizophrenia. Differences between studies could come from the different task included in the composite score representing EF. Indeed the "Executive Performance" domain from Fiksinski et al. was derived from a principal component analyses including tasks not only evaluating EF, while test from Weinberger et al. were selected a priori to target EF.

An alternative approach taking advantage of longitudinal data is to investigate the predictive value of selected cognitive indicators. In a prospective study, lower performance on measures of flexibility, planning and attention during childhood predicted more prodromal symptoms in adolescence (Antshel et al., 2010). Moreover, in a study from the same group investigating trajectories of performance over time, individuals with 22q11DS who developed prodromal/overt psychotic symptoms improved less with time on a measure of cognitive flexibility (Antshel et al., 2017). Interestingly in this study, although trajectories of several cognitive domains (reading, mathematics, EF, attention, learning) were included in the analyses, only EF (cognitive flexibility) and reading abilities had divergent trajectories in participants who developed prodromal or overt psychosis. Similarly, Study 1 also investigated if 22q11DS participants displaying psychotic symptoms had atypical trajectories of improvement with age. Indeed, minimal improvement of performance with age of inhibition

and working memory measures was found in 22q11DS participants who displayed negative psychotic symptoms. No association was found with positive psychotic symptoms. Taken together, results from previous studies and our own, suggest that the trajectories of improvement with age of some EF sub-domains bear a predictive value for the development of psychotic symptoms in the future. Furthermore, previous work demonstrated that impairment in sub-domains of EF (initiation and multitasking) is associated with the severity of negative psychotic symptoms in 22q11DS (Dubourg, Maeder, Pouillard, Eliez, & Schneider, 2020; Schneider et al., 2016). Even though the literature reviewed here implies that executive dysfunction could underlie the development of psychotic symptoms, further understanding of the cognitive mechanism is still needed.

2.3. Evidence for subgroups

Despite a relatively homogenous genetic origin, the heterogeneity of the phenotype of 22q11DS has been extensively documented (Philip & Bassett, 2011; Robin & Shprintzen, 2005; Swillen & McDonald-McGinn, 2015). Yet only a handful of studies have focused on the identification of subgroups of patients based on different variables. As summarized by Swillen (2016), several factors influencing variability of intellectual ability have been investigated such as origin of the deletion (*de novo* or familial), genetic variation within the 22q11.2 region, gender effect, or environmental effects (e.g., socioeconomic status, parental IQ). Focusing on the symptomatology of psychosis, Schneider, van der Linden et al. (2014) examined the distribution of positive and negative psychotic symptoms in a population of 63 adolescents and young adults with 22q11DS using a cluster analysis. Individuals with predominantly negative symptoms had significantly lower visual memory scores (face recognition) and decreased processing speed compared to participants with low levels of symptoms. Building on these results, Mihailov et al. (2017) found that 22q11DS participants with higher negative symptoms also displayed gyrification reductions predominantly in medial occipital and temporal regions

of the brain. In a more global approach, Sinderberry et al. (2013) investigate whether subtypes of patients with 22q11DS can be identified presenting with a similar phenotype and an increased risk of developing mental health problems. Using a k-means clustering approach in a sample of 50 children and adolescents (6-17 years old) with 22q11DS, they found evidence for two distinct subtypes. The first one substantially more affected (showing reductions in total brain volume; lower intellectual functioning; poorer mathematical ability, verbal skills, and verbal memory; and increased autistic-like traits, including poor social skills), than the second (more significant executive function deficits and more typical 22q11DS facial features). However, the extensive range of variables selected for the cluster analysis (including cognitive measures along with brain volume, physical facial features and psychiatric symptoms together) and the modest sample (N=50) with a broad age range (6-17 years old) limits the clinical relevance and possibility to expand the results.

In all the studies presented in the empirical section, a great variability in cognitive performance appears very clearly. In Study 3, one attempt to identify subgroups was put forward using a clustering approach on memory retention performance. This approach revealed useful information by identifying a subgroup of 22q11DS patients with faster memory forgetting rates associated with lower intellectual functioning, higher rates of positive psychotic symptoms and hippocampal volume reduction. Although challenging because of the protracted development, future work should investigate if patterns of executive dysfunction could be found in 22q11DS and relate to psychiatric outcome.

3. Limits

The work presented here should be considered in light of a few limitations. First of all, across the studies compiled here, the age range represented only one section of the lifespan, from school-age children to young adults. Indeed, the data presented comes from the Swiss

longitudinal cohort which focuses on childhood and adolescence. Therefore, participants older than 35 years old are only rarely included, limiting power for statistical analysis. Literature on adults with 22q11DS older than 30 is still scarce, nevertheless, improvement in the care and reduced mortality rate leads to new challenges. For example, there is evidence for early-onset of neurodegenerative disorders (such as Parkinson's disease), increasing the risk for cognitive decline in this population (Butcher et al., 2013; Fung et al., 2015). It becomes clear that the next step for the developmental trajectories of cognitive measures presented here is to include the whole lifespan to examine patterns of development and decline.

A second limitation is the absence of investigation of the relationship between cognitive performance and specific genes. Indeed, relationship between reduced gene-dosage and the complex clinical picture of 22q11DS has received a lot of attention. One well studied example is the gene encoding for catechol-o-methyltransferase (COMT) which is responsible for degrading the catecholamines dopamine, norepinephrine, and epinephrine. Although COMT is expressed in several parts of the brain, it is particularly important for dopamine flux in the PFC (Chen et al., 2004). Therefore, COMT haploinsufficiency has been suggested to play a role in the pathways leading to cognitive impairment and psychiatric disorders (Gothelf et al., 2008). However the association of COMT polymorphism and the specific neurocognitive profile of 22q11DS needs further investigations (for a review see Armando, Papaleo, & Vicari, 2012).

Finally, this work does not include a developmental perspective on memory, as it does for EF and attention processes. By investigating memory functioning from 8 years old, memory mechanism are almost mature with most development occurring before the age of 9 (Picard, Cousin, Guillery-Girard, Eustache, & Piolino, 2012). In future work, developmental patterns of memory retention processes should be investigated in young children (<8 years old).

4. Conclusions

In sum, the work compiled in this thesis had two main objectives, the first one more descriptive and the second one more practical. In the first part, the objective was to specify and extend knowledge on the neuropsychological profile of 22q11DS, with a focus on EF and memory. Study 1 and 2 provided a picture of developmental patterns of maturation of multiple sub-domains of EF and attention. Different developmental patterns were demonstrated across the sub-domains examined, highlighting the necessity to administer extensive, multi-facetted evaluations to have a more reliable overview of 22q11DS patients' cognitive profile. In Study 3 and 4, memory retention was investigated over long delays in time to capture trajectories of forgetting over a one-month time laps. Faster forgetting rates were observed in the 22q11DS group compared to controls for both verbal and non-verbal information (when correcting for learning performance). Similarly, to the control group, multiple recalls in time at different delays slowed down the pace of forgetting. Results highlight potential strategies to implement for maintaining memory over long delays.

In the second part, the objective was to move past the description of observed deficits or atypical developmental pattern to evaluate a type of intervention by examining the effect of medication on the cognitive processes described previously. Inspired by the high rates of ADHD observed in 22q11DS, a clinical trial examining the benefits of a stimulant medication (methylphenidate) was conducted in Study 5. The results are encouraging as they showed improvement of core ADHD symptoms (primarily inattention symptoms) as well as a selection of cognitive function (attention, inhibition and potentially processing speed). Furthermore, in a subgroup of patients naïve to the molecule, treatment was found to be safe with regards to cardiac values, and while side effects were frequent, they remained of mild intensity.

On a larger scale, the results compiled in this thesis have implications for research and clinical practice. On the research level, we bring an in-depth analysis of deficits related to EF and

memory clarifying inconsistent results in the literature. Furthermore, we developed adapted tools to answer our research question regarding memory and forgetting, where previous research findings contrasted with patients' and caregivers' observations. On the clinical practice level, this work provides insight into strength and weaknesses of the cognitive profile to suggest a suitable educational and professional project for individuals with 22q11DS. Results could be used to develop suitable working strategies or tailored intervention programs. Finally, our research participates in the knowledge used to develop recommendations for the management and care of individuals with 22q11DS, including the use of medication.

IV. SUPPLEMENTARY METERIAL

Supplementary material for Study 2

Table S1: Details of the measures of executive function and attention and information about missing data

Cognitive domain	Test name	Variable name	Description	Interpretation	Missing data
Visual attention	Conners' Continuous Performance Test (CPT 2nd and 3rd editions) (Conners & MHS Staff, 2000, 2014)	*CPT omission %*	Percentage of omission errors, with omissions defined as missed targets	Lower score is better	6 participants (4 with 22q11DS) 2 because of lack of time 4 scores were not calculated by the program due to validity issues with the evaluation
	Color Trails Test (D'Elia & Satz, 1989)	*Adjusted time part A*	Time to complete part A where participants are asked to draw a line between number following chronological order. Since 2 versions of the test were used with increasing level of difficulty (8-16 years old = 15 numbers to connect; from 17 years old = 25 numbers to connect) we adjusted the score by dividing the time to complete part A by the number of items to connect	Lower score is better	4 participants (2 with 22q11DS) due to errors in the administration of the test
	Symbol Search, Wechsler intelligence scales (Wechsler, 1997a, 2004, 2011, 2016)	*Number of symbols*	Raw score of items correctly identified (either recognized or with a yes/no answer)	Higher score is better	No missing data
Inhibition	Stroop task (Albaret & Migliore, 1999),	*Stroop inhibition ratio*	Inhibition ratio calculated to measure the cost of inhibition by dividing the number of colors named in the interference condition (naming the color of the ink of the word during 45 seconds), by the number of colors named in the color denomination condition (naming rectangles of colors during 45 seconds) (see Maeder et al., 2016)	Value closer to 1 indicate better inhibition	7 participants (5 with 22q11DS) due to technical errors in the administration of the task
	Conners' Continuous Performance Test (CPT 2nd and 3rd editions)	*CPT commission %*	Percentage of commission errors was extracted. Commission errors are defined as incorrect responses to non-targets	Lower score is better	6 participants (4 with 22q11DS) 2 because of lack of time 4 scores were not calculated by the program due to validity issues with the evaluation
	Stop-Signal Task (SST, CANTAB) (Cambridge Cognition Ltd., 2013)	*Stop-Signal RT*	Estimate of the length of time between the go stimulus and the stop stimulus at which the participant is able to successfully inhibit his response on 50% of trials	Lower score is better	14 participants (6 with 22q11DS) due to the malfunction of a cable
Flexibility	Color Trails Test (D'Elia & Satz, 1989)	*Flexibility ratio*	Flexibility ratio was calculated to account for processing speed by dividing the time to complete part B (drawing a line between number following chronological order while alternating between colors) by time to complete part A (drawing a line between number following chronological order)	Value closer to 1 indicate better flexibility	4 participants (2 with 22q11DS) due to errors in the administration of the test
	Intra-/Extra-Dimensional Shift task (IED, CANTAB) (Cambridge Cognition Ltd., 2013)	*EDS errors*	Number of extra-dimensional shift errors	Lower score is better	1 control participant was excluded because of a lack of comprehension of the instruction (only completed 1/9 stages).

Updating	Digit Span, Wechsler intelligence scales (Wechsler, 1997a, 2004, 2011, 2016)	*Backward span*	Longest sequence of numbers repeated in invers order	Higher score is better	No missing data
	Letter-Number Sequencing, Wechsler intelligence scales (Wechsler, 1997a, 2004, 2011, 2016)	*Letter-number span*	Longest sequence of letters and numbers correctly ordered	Higher score is better	No missing data
	Spatial Working Memory (SWM, CANTAB) (Cambridge Cognition Ltd., 2013)	*Total between error Between error 4,6,8 boxes*	Number of times the participant revisits a box in which a token has previously been found. Three different memory loads (4, 6, 8 boxes)	Lower score is better	No missing data
Initiation	Verbal fluency task (animal category)	*Number of animals*	Number of different animal names produced under one minute	Higher score is better	3 participants (2 with 22q11DS) due to a lack of time
	Non-verbal fluency task (5 points task, Sevino, 1998)	*Number of designs*	Number of different designs produced under three minutes	Higher score is better	12 participants (9 with 22q11DS) 9 due to a lack of time 4 difficulties following the instructions given by the examiner

Supplementary material for Study 3

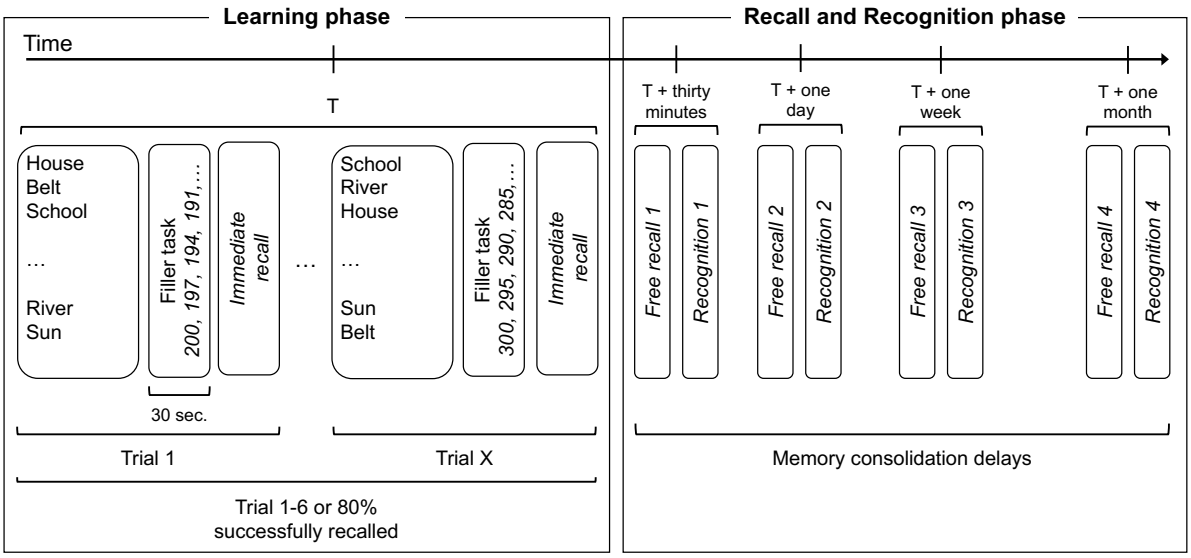

Figure S1: Displaying the different steps of the long-term episodic memory task.

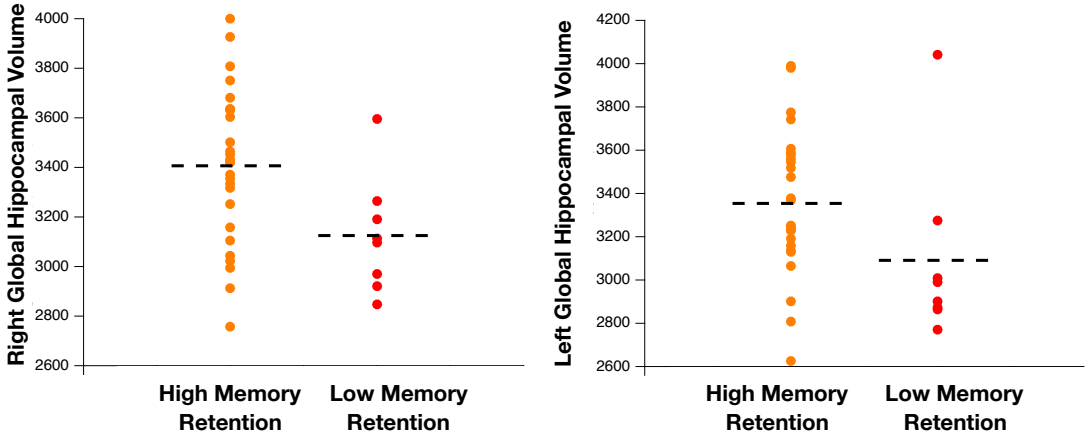

Figure S2: Values of right and left global hippocampal volume in individuals divided according to trajectories of normalized memory retention. Dashed lines indicate mean volume in each subgroup.

Table S1: Rey Auditory Verbal Learning Task (RAVLT), four parallel lists, in French/*English*:

List A	List B	List C	List D
Tambour/*Drum*	Pupitre/*Desk*	Orange/*Orange*	Violon/*Violin*
Rideau/*Curtain*	Berger/*Shepherd*	Fauteuil/*Chair*	Arbre/*Tree*
Ceinture/*Belt*	Moineau/*Sparrow*	Crapaud/*Toad*	Cravate/*Tie*
Café/*Coffee*	Soulier/*Shoe*	Bouchon/*Cork*	Jambon/*Ham*
École/*School*	Fourneau/*Stove*	Voiture/*Car*	Valise/*Suitcase*
Parent/*Parent*	Montagne/*Mountain*	Menton/*Chin*	Cousin/*Cousin*
Soleil/*Sun*	Lunette/*Glasses*	Rivage/*Shore*	Oreille/*Ear*
Jardin/*Garden*	Éponge/*Sponge*	Savon/*Soap*	Couteau/*Knife*
Casquette/*Cap*	Image/*Image*	Hôtel/*Hotel*	Escalier/*Stairs*
Paysan/*Farmer*	Bateau/*Boat*	Cheval/*Horse*	Chien/*Dog*
Moustache/*Moustache*	Mouton/*Sheep*	Insecte/*Insect*	Banane/*Banana*
Dindon/*Turkey*	Fusil/*Rifle*	Toilette/*Toilet*	Outil/*Tool*
Couleur/*Colour*	Crayon/*Pen*	Marmite/*Pot*	Chasseur/*Hunter*
Maison/*House*	Église/*Church*	Soldat/*Soldier*	Seau/*Bucket*
Rivière/*River*	Poisson/*Fish*	Serrure/*Lock*	Campagne/*Countryside*

Table S2: Recognition task example: List A, Recognition 1, in French/*English*:

Piano/*Piano*	Y	N	Tête/*Head*	Y	N
Tambour/*Drum*	Y	N	Jardin/*Garden*	Y	N
Tapis/*Carpet*	Y	N	Soleil/*Sun*	Y	N
Manteau/*Coat*	Y	N	Maçon/*Builder*	Y	N
Matin/*Morning*	Y	N	Bouche/*Mouth*	Y	N
Rideau/*Curtain*	Y	N	Casquette/*Cap*	Y	N
Frère/*Brother*	Y	N	Oiseau/*Bird*	Y	N
École/*School*	Y	N	Paysan/*Farmer*	Y	N
Plage/*Beach*	Y	N	Lueur/*Glow*	Y	N
Punition/*Punishment*	Y	N	Parent/*Parent*	Y	N
Ceinture/*Belt*	Y	N	Moustache/*Moustache*	Y	N
Maison/*House*	Y	N	Chambre/*Room*	Y	N
Sapin/*Fir*	Y	N	Dindon/*Turkey*	Y	N
Café/*Coffee*	Y	N	Eau/*Water*	Y	N
Rivière/*River*	Y	N	Couleur/*Colour*	Y	N

NB: target words are underlined and the correct answer (Yes/No) is marked in grey.

Table S3: Examples of phonemic and semantic distractors from the recognition part of the task, in French/*English*:

Target word	**Phonemic distractor**	**Semantic distractor**
Banane/*Banana*	Cabane/*Hut*	Poire/*Pear*
Soldat/*Soldier*	Panda/*Panda*	Guerre/*War*
Bouchon/*Cork*	Balluchon/*Bundle*	Couvercle/*Lid*

Supplementary material for Study 5

Table S1: Raw measures of response speed, variability of response speed, omission and commission errors across all 6 blocks

			WITHOUT			WITH			Wilcoxon signed rank test		Effect size	B-H correction
Test	Variable (raw scores)		Mean	SD	Median	Mean	SD	Median	*Z*	*p*	*r*	Adjusted p
CPT-3	Hit RT	Block 1	411,5	118,26	383	381,86	110,281	351	-1,948	0,051	0,29	0,007
		Block 2	436	152,85	370	405,05	133,596	365	-2,192	0,028	0,33	0,013
		Block 3	441,23	154,18	381	414,73	121,389	365	-0,796	0,426	0,12	0,003
		Block 4	449,23	131,38	390	398,5	103,917	373	-2,312	0,021	0,35	0,014
		Block 5	515,77	14,50	424	398,45	84,698	389,5	-4,107	**0,000**	0,62	0,025
		Block 6	459,82	129,39	441,5	406,82	91,096	368,5	-3,100	**0,002**	0,47	0,020
	Hit RT SD	Block 1	212,55	226,99	98	111,82	130,446	68	-3,198	**0,001**	0,48	0,023
		Block 2	262,86	234,38	171	143,41	163,706	91	-3,555	**0,000**	0,54	0,024
		Block 3	224,82	211,64	121	133,91	112,372	87,5	-2,646	**0,008**	0,40	0,017
		Block 4	236,95	175,75	185,5	154,14	136,788	102,5	-2,646	**0,008**	0,40	0,016
		Block 5	304,32	288,74	179,5	157,32	115,379	102,5	-3,036	**0,002**	0,46	0,019
		Block 6	274,68	192,39	225	140,14	94,481	99,5	-3,215	**0,001**	0,48	0,022
	Omissions	Block 1	5,05	6,925	2	2,86	5,592	0	-2,791	**0,005**	0,42	0,018
		Block 2	7,09	12,20	4	3,5	5,484	1	-2,17	0,030	0,33	0,010
		Block 3	8,59	13,32	4	3,5	5,638	2	-2,199	0,028	0,33	0,011
		Block 4	7,73	11,15	4	2,91	4,363	1	-2,462	**0,014**	0,37	0,015
		Block 5	9,77	14,50	5	4,86	8,397	2	-2,068	0,039	0,31	0,008
		Block 6	10,18	9,29	8	3,14	4,004	1	-3,43	**0,001**	0,52	0,021
	Commissions	Block 1	55,36	17,38	50	50,77	23,676	50	-0,764	0,445	0,12	0,001
		Block 2	57,18	22,31	62,5	45,14	21,634	42	-2,077	0,038	0,31	0,009
		Block 3	51,59	19,37	50	46,95	22,5	50	-0,768	0,443	0,12	0,002
		Block 4	59,05	19,35	58	51,05	24,045	50	-1,29	0,197	0,19	0,004
		Block 5	56,09	18,80	58	47,27	20,055	50	-1,953	0,051	0,29	0,006
		Block 6	59,41	20,06	62,5	47	23,775	50	-1,877	0,061	0,28	0,005

NB: RT = Reaction Time; SD = Standard Deviation

Significant p-values after Benjamini-Hochberg (B-H) correction are displayed in **bold**

V. BIBLIOGRAPHY

Akshoomoff, N., Newman, E., Thompson, W. K., McCabe, C., Bloss, C. S., Chang, L., … Jernigan, T. L. (2014). The NIH toolbox cognition battery: Results from a large normative developmental sample (PING). *Neuropsychology*, 28(1), 1–10. Retrieved from https://doi.org/10.1037/neu0000001

Albaret, J. M., & Migliore, L. (1999). *Stroop test d'attention sélective de Stroop*. Paris: ECPA.

Alberini, C. M., & Ledoux, J. E. (2013). Memory reconsolidation. *Current Biology*, 23(17), R746–R750. Retrieved from https://doi.org/10.1007/7854_2016_463

Albert, A. B., Abu-Ramadan, T., Kates, W. R., Fremont, W., & Antshel, K. M. (2018). Childhood Executive Functioning Predicts Young Adult Outcomes in 22q11.2 Deletion Syndrome. *Journal of the International Neuropsychological Society*, 24(9), 905–916. Retrieved from https://doi.org/10.1017/S1355617718000784

American Psychiatric Association. (2013). *Diagnostic and Statistical Manual of Mental Disorders* (5th ed.). Arlington, VA.

Anderson, P. (2002). Assessment and development of executive function (EF) during childhood. *Child Neuropsychology*, 8(March 2015), 71–82. Retrieved from https://doi.org/10.1076/chin.8.2.71.8724

Anderson, P., & Reidy, N. (2012). Assessing executive function in preschoolers. *Neuropsychology Review*, 22, 345–360. Retrieved from https://doi.org/10.1007/s11065-012-9220-3

Angkustsiri, K., Leckliter, I., Tartaglia, N., Beaton, E. A., Enriquez, J., & Simon, T. J. (2012). An Examination of the Relationship of Anxiety and Intelligence to Adaptive Functioning in Children with Chromosome 22q11.2 Deletion Syndrome. *Journal of Developmental & Behavioral Pediatrics*, 33(9), 713–720. Retrieved from

https://doi.org/10.1097/DBP.0b013e318272dd24

Antoniades, M., Schoeler, T., Radua, J., Valli, I., Allen, P., Kempton, M. J., & McGuire, P. (2017). Verbal learning and hippocampal dysfunction in schizophrenia: A meta-analysis. *Neuroscience and Biobehavioral Reviews*, (March), 0–1. Retrieved from https://doi.org/10.1016/j.neubiorev.2017.12.001

Antshel, K. M., Faraone, S. V., Fremont, W., Monuteaux, M. C., Kates, W. R., Doyle, A., … Biederman, J. (2007). Comparing ADHD in Velocardiofacial Syndrome to Idiopathic ADHD. *Journal of Attention Disorders*, 11(1), 64–73. Retrieved from https://doi.org/10.1177/1087054707299397

Antshel, K. M., Fremont, W., & Kates, W. R. (2008). The neurocognitive phenotype in velo-cardio-facial syndrome: A developmental perspective. *Developmental Disabilities Research Reviews*, 14(January), 43–51. Retrieved from https://doi.org/10.1002/ddrr.7

Antshel, K. M., Fremont, W., Ramanathan, S., & Kates, W. R. (2017). Predicting Cognition and Psychosis in Young Adults With 22q11.2 Deletion Syndrome. *Schizophrenia Bulletin*, 43(4), sbw135. Retrieved from https://doi.org/10.1093/schbul/sbw135

Antshel, K. M., Fremont, W., Roizen, N. J., Shprintzen, R., Higgins, A. M., Dhamoon, A., & Kates, W. R. (2006). ADHD, major depressive disorder, and simple phobias are prevalent psychiatric conditions in youth with velocardiofacial syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry*, 45(5), 596–603. Retrieved from https://doi.org/10.1097/01.chi.0000205703.25453.5a

Antshel, K. M., Hendricks, K., Shprintzen, R., Fremont, W., Higgins, A. M., Faraone, S. V., & Kates, W. R. (2013). The longitudinal course of attention deficit/hyperactivity disorder in velo-cardio-facial syndrome. *Journal of Pediatrics*, 163(1), 187-193.e1. Retrieved from https://doi.org/10.1016/j.jpeds.2012.12.026

Antshel, K. M., Peebles, J., AbdulSabur, N., Higgins, A. M., Roizen, N., Shprintzen, R., …

Kates, W. R. (2008). Associations between performance on the Rey-Osterrieth complex figure and regional brain volumes in children with and without velocardiofacial syndrome. *Developmental Neuropsychology*, 33(5), 601–622. Retrieved from https://doi.org/10.1080/87565640802254422

Antshel, K. M., Shprintzen, R. J., Fremont, W., Higgins, A. M., Faraone, S. V., & Kates, W. R. (2010). Cognitive ans Psychiatric Predictors to Psychosis in Velocardiofacial Syndrome: A 3-year follow-up study. *Journal of American Academy of Child Ans Adolescent Psychiatry*, 49(4), 333–344.

Armando, M., Ciampoli, M., Padula, M. C., Amminger, P., De Crescenzo, F., Maeder, J., … Papaleo, F. (2020). Favorable effects of omega-3 polyunsaturated fatty acids in attentional control and conversion rate to psychosis in 22q11.2 deletion syndrome. *Neuropharmacology*, 168(August 2019), 107995. Retrieved from https://doi.org/10.1016/j.neuropharm.2020.107995

Armando, M., Papaleo, F., & Vicari, S. (2012). COMT Implication in Cognitive and Psychiatric Symptoms in Chromosome 22q11 Microdeletion Syndrome: A Selective Review. *CNS & Neurological Disorders - Drug Targets*, 11(3), 273–281. Retrieved from https://doi.org/10.2174/187152712800672526

Armando, M., Sandini, C., Chambaz, M., Schaer, M., Schneider, M., & Eliez, S. (2018). Coping Strategies Mediate the Effect of Stressful Life Events on Schizotypal Traits and Psychotic Symptoms in 22q11.2 Deletion Syndrome. *Schizophrenia Bulletin*, 44(2), 525–535. Retrieved from https://doi.org/10.1093/schbul/sby025

Attout, L., Noël, M., Vossius, L., & Rousselle, L. (2017). Evidence of the impact of visuo-spatial processing on magnitude representation in 22q11.2 microdeletion syndrome. *Neuropsychologia*, 99, 296–305. Retrieved from https://doi.org/10.1016/j.neuropsychologia.2017.03.023

Azuma, R., Daly, E. M., Campbell, L. E., Stevens, A. F., Deeley, Q., Giampietro, V., … Murphy, K. C. (2009). Visuospatial working memory in children and adolescents with 22q11.2 deletion syndrome; An fMRI study. *Journal of Neurodevelopmental Disorders*, 1(1), 46–60. Retrieved from https://doi.org/10.1007/s11689-009-9008-9

Badoud, D., Schneider, M., Menghetti, S., Glaser, B., Debbané, M., & Eliez, S. (2017). Understanding others : a pilot investigation of cognitive and affective facets of social cognition in patients with 22q11.2 deletion syndrome (22q11DS). *Journal of Neurodevelopmental Disorders*, 9(35), 1–9. Retrieved from https://doi.org/10.1186/s11689-017-9216-7

Banaschewski, T., Coghill, D., Santosh, P., Zuddas, A., Asherson, P., Buitelaar, J., … Taylor, E. (2006). Long-acting medications for the hyperkinetic disorders: A systematic review and European treatment guideline. *European Child and Adolescent Psychiatry*, 15(8), 476–495. Retrieved from https://doi.org/10.1007/s00787-006-0549-0

Barkley, R. A., Fischer, M., Newby, R. F., & Breen, M. J. (1988). Development of a Multimethod Clinical Protocol for Assessing Stimulant Drug Response in Children With Attention Deficit Disorder. *Journal of Clinical Child Psychology*, 17(1), 14–24. Retrieved from https://doi.org/10.1207/s15374424jccp1701_3

Bearden, C. E., Woodin, M. F., Wang, P. P., Moss, E., Zackai, E., Emannuel, B., … Neurocognitive, T. (2001). The Neurocognitive Phenotype of the 22Q11 . 2 Deletion Syndrome : Selective Deficit in Visual-Spatial Memory. *Journal of Clinical and Experimental Neuropsychology*, 23(4), 447–464. Retrieved from https://doi.org/10.1076/jcen.23.4.447.1228

Besseau-Ayasse, J., Violle-Poirsier, C., Bazin, A., Gruchy, N., Moncla, A., Girard, F., … Vialard, F. (2014). A French collaborative survey of 272 fetuses with 22q11.2 deletion: ultrasound findings, fetal autopsies and pregnancy outcomes. *Prenatal Diagnosis*, 34(5),

424–430. Retrieved from https://doi.org/10.1002/pd.4321

Best, J. R., & Miller, P. H. (2010). A developmental perspective on executive function. *Child Development*, 81(6), 1641–1660. Retrieved from https://doi.org/10.1111/j.1467-8624.2010.01499.x

Bisaz, R., Travaglia, A., & Alberini, C. M. (2014). The neurobiological bases of memory formation: From physiological conditions to psychopathology. *Psychopathology*, 47(6), 347–356. Retrieved from https://doi.org/10.1159/000363702

Bora, E., & Murray, R. M. (2014). Meta-analysis of cognitive deficits in ultra-high risk to psychosis and first-episode psychosis: Do the cognitive deficits progress over, or after, the onset of psychosis? *Schizophrenia Bulletin*, 40(4), 744–755. Retrieved from https://doi.org/10.1093/schbul/sbt085

Bostelmann, M., Glaser, B., Zaharia, A., Eliez, S., & Schneider, M. (2017). Does differential visual exploration contribute to visual memory impairments in 22q11 . 2 microdeletion syndrome ? *Journal of Intellectual Disability Research*, 61(12), 1174–1184. Retrieved from https://doi.org/10.1111/jir.12440

Bostelmann, M., Schneider, M., Padula, M. C., Maeder, J., Schaer, M., Scariati, E., … Eliez, S. (2016). Visual memory profile in 22q11.2 microdeletion syndrome: Are there differences in performance and neurobiological substrates between tasks linked to ventral and dorsal visual brain structures? A cross-sectional and longitudinal study. *Journal of Neurodevelopmental Disorders*, 8(1), 1–13. Retrieved from https://doi.org/10.1186/s11689-016-9174-5

Botto, L. D., May, K., Fernhoff, P. M., Correa, A., Coleman, K., Rasmussen, S., … Campbell, R. M. (2003). A Population-Based Study of the 22q11.2 Deletion: Phenotype, Incidence, and Contribution to Major Birth Defects in the Population. *Pediatrics*, 112(1), 101–108.

Brown, R. G., & Pluck, G. (2000). Negative symptoms: the 'pathology' of motivation and

goal-directed behaviour. *Trends in Neurosciences*, 23(9), 412–417. Retrieved from https://doi.org/10.1016/S0166-2236(00)01626-X

Burgess, P. W., Alderman, N., Evans, J., Emslie, H., & Wilson, B. A. (1998). The ecological validity of tests of executive function. *Journal of the International Neuropsychological Society*, 4(6), 547–558. Retrieved from https://doi.org/10.1017/S1355617798466037

Butcher, N. J., Kiehl, T.-R., Hazrati, L.-N., Chow, E. W. C., Rogaeva, E., Lang, A. E., & Bassett, A. S. (2013). Association Between Early-Onset Parkinson Disease and 22q11.2 Deletion Syndrome. *JAMA Neurology*, 70(11), 1359. Retrieved from https://doi.org/10.1001/jamaneurol.2013.3646

Cambridge Cognition Ltd. (2013). CANTABeclipse 6, Test Adminstration Guide. Cambridge: Cambridge Cognition Ltd.

Campbell, I. M., Sheppard, S. E., Crowley, T. B., McGinn, D. E., Bailey, A., McGinn, M. J., … McDonald-McGinn, D. M. (2018). What is new with 22q? An update from the 22q and You Center at the Children's Hospital of Philadelphia. *American Journal of Medical Genetics, Part A*, 176(10), 2058–2069. Retrieved from https://doi.org/10.1002/ajmg.a.40637

Campbell, L. E., Azuma, R., Ambery, F., Stevens, A., Smith, A., Morris, R. G., … Murphy, K. C. (2010). Executive functions and memory abilities in children with 22q11.2 deletion syndrome. *The Australian and New Zealand Journal of Psychiatry*, 44(4), 364–371. Retrieved from https://doi.org/10.3109/00048670903489882

Campbell, L. E., McCabe, K. L., Melville, J. L., Strutt, P. A., & Schall, U. (2015). Social cognition dysfunction in adolescents with 22q11.2 deletion syndrome (velo-cardio-facial syndrome): Relationship with executive functioning and social competence/functioning. *Journal of Intellectual Disability Research*, 59(9), 845–859. Retrieved from https://doi.org/10.1111/jir.12183

Campbell, L. E., Stevens, A., Daly, E., Toal, F., Azuma, R., Karmiloff-Smith, A., … Murphy, K. C. (2009). A comparative study of cognition and brain anatomy between two neurodevelopmental disorders: 22q11.2 deletion syndrome and Williams syndrome. *Neuropsychologia*, 47(4), 1034–1044. Retrieved from https://doi.org/10.1016/j.neuropsychologia.2008.10.029

Cancrini, C., Puliafito, P., Digilio, M. C., Soresina, A., Martino, S., Rondelli, R., … Rossi, P. (2014). Clinical features and follow-up in patients with 22q11.2 deletion syndrome. *Journal of Pediatrics*, 164(6), 1475-1480.e2. Retrieved from https://doi.org/10.1016/j.jpeds.2014.01.056

Cannon, T. D. (2005). The inheritance of intermediate phenotypes for schizophrenia. *Current Opinion in Psychiatry*, 18, 135–140.

Cantonas, L. M., Tomescu, M. I., Biria, M., Jan, R. K., Schneider, M., Eliez, S., … Michel, C. M. (2019). Abnormal development of early auditory processing in 22q11.2 Deletion Syndrome. *Translational Psychiatry*, 9(1), 15–17. Retrieved from https://doi.org/10.1038/s41398-019-0473-y

Chawner, S. J. R. A., Doherty, J. L., Moss, H., Niarchou, M., Walters, J. T. R., Owen, M. J., & van den Bree, M. B. M. (2017). Childhood cognitive development in 22q11.2 deletion syndrome: case-control study. *The British Journal of Psychiatry : The Journal of Mental Science*, 211(4), 223–230. Retrieved from https://doi.org/10.1192/bjp.bp.116.195651

Chen, J., Lipska, B. K., Halim, N., Ma, Q. D., Matsumoto, M., Melhem, S., … Weinberger, D. R. (2004). Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): Effects on mrna, protein, and enzyme activity in postmortem human brain. *American Journal of Human Genetics*, 75(5), 807–821. Retrieved from https://doi.org/10.1086/425589

Chow, E. W. C., Watson, M., Young, D. A., & Bassett, A. S. (2006). Neurocognitive profile

in 22q11 deletion syndrome and schizophrenia. *Schizophrenia Research*, 87(1–3), 270–278. Retrieved from https://doi.org/10.1016/j.schres.2006.04.007

Clark, L. K., Warman, D., & Lysaker, P. H. (2010). The relationships between schizophrenia symptom dimensions and executive functioning components. *Schizophrenia Research*, 124(1–3), 169–175. Retrieved from https://doi.org/10.1016/j.schres.2010.08.004

Clark, R. E., & Martin, S. J. (2018). *Behavioral Neuroscience of Learning and Memory*. (R.E. Clark & S.J. Martin,Eds.), *Current Topics in Behavioral Neurosciences* (Vol. 37). Cham: Springer International Publishing. Retrieved from https://doi.org/10.1007/978-3-319-78757-2

Coghill, D. R., Seth, S., Pedroso, S., Usala, T., Currie, J., & Gagliano, A. (2014). Effects of methylphenidate on cognitive functions in children and adolescents with attention-deficit/hyperactivity disorder: Evidence from a systematic review and a meta-analysis. *Biological Psychiatry*, 76(8), 603–615. Retrieved from https://doi.org/10.1016/j.biopsych.2013.10.005

Cohen, M. (1997). *Children's Memory Scale*. London: Psychological Corporation.

Conners, C. K., & MHS Staff. (2000). *Conners Continuous Performance Test II: Computer program for Windows technical guide and software manual*. North Tonawanda, NY: Multi-Health Systems.

Conners, C. K., & MHS Staff. (2014). *Conners Continuous Performance Test 3rd edition: Technical manual*. North Tonawanda, NY: Multi-Health Systems.

Cortese, S., Adamo, N., Del Giovane, C., Mohr-Jensen, C., Hayes, A. J., Carucci, S., … Cipriani, A. (2018). Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: a systematic review and network meta-analysis. *The Lancet Psychiatry*, 5(9), 727–738. Retrieved from https://doi.org/10.1016/S2215-0366(18)30269-4

Costanzo, F., Varuzza, C., Menghini, D., Addona, F., Gianesini, T., & Vicari, S. (2013). Executive functions in intellectual disabilities: A comparison between Williams syndrome and Down syndrome. *Research in Developmental Disabilities*, 34(5), 1770–1780. Retrieved from https://doi.org/10.1016/j.ridd.2013.01.024

Culbertson, W. C., & Zillmer, E. A. (1999). *The Tower of London, Drexel University, research version: Examiner's manual*. North Tonawanda, NY: Multi-Health Systems.

Cutler-Landsman, D. (2020). *Educating Children with Velo-Cardio-Facial Syndrome, 22q11.2 Deletion Syndrome, and DiGeorge Syndrome*. (D. Cutler-Landsman,Ed.) (third edit). San Diego, CA: Plural Publishing Inc.

D'Elia, L. F., & Satz, P. (1989). *Color Trails Test*. Odessa(FL): Psychological Assessment Resources, Inc.

Da Silva Alves, F., Schmitz, N., Bloemen, O., van der Meer, J., Meijer, J., Boot, E., … van Amelsvoort, T. (2011). White matter abnormalities in adults with 22q11 deletion syndrome with and without schizophrenia. *Schizophrenia Research*, 132(1), 75–83. Retrieved from https://doi.org/10.1016/j.schres.2011.07.017

de Smedt, B., Swillen, A., Devriendt, K., Fryns, J. P., Verschaffel, L., & Ghesqui, P. (2007). Mathematical disabilities in children with velo-cardio-facial syndrome. *Neuropsychologia*, 45, 885–895. Retrieved from https://doi.org/10.1016/j.neuropsychologia.2006.08.024

de Smedt, B., Swillen, A., Verschaffel, L., & Ghesquière, P. (2009). Mathematical learning disabilities in children with 22q11.2 deletion syndrome: A review. *Developmental Disabilities Research Reviews*, 15(1), 4–10. Retrieved from https://doi.org/10.1002/ddrr.44

de Sonneville, L. M. J., Hidding, E., van Engeland, H., Vorstman, J. A. S., Sijmens-Morcus, M. E. J., & Swaab, H. (2018). Executive functioning and its relation to ASD and ADHD

symptomatology in 22q11.2 deletion syndrome*. *Child Neuropsychology*, 24(1), 1–19. Retrieved from https://doi.org/10.1080/09297049.2016.1221064

Debbané, M., Glaser, B., & Eliez, S. (2008). Encoding and Retrieval Processes in Velo-Cardio-Facial Syndrome (VCFS). *Neuropsychology*, 22(2), 226–234. Retrieved from https://doi.org/10.1037/0894-4105.22.2.226

Debbané, M., Schaer, M., Farhoumand, R., Glaser, B., & Eliez, S. (2006). Hippocampal volume reduction in 22q11.2 deletion syndrome. *Neuropsychologia*, 44(12), 2360–2365. Retrieved from https://doi.org/10.1016/j.neuropsychologia.2006.05.006

DeBoer, T., Wu, Z., Lee, A., & Simon, T. J. (2007). Hippocampal volume reduction in children with chromosome 22q11.2 deletion syndrome is associated with cognitive impairment. *Behavioral and Brain Functions*, 3, 1–9. Retrieved from https://doi.org/10.1186/1744-9081-3-54

Dedrick, R. F., Ferron, J. M., Hess, M. R., Hogarty, K. Y., Kromrey, J. D., Lang, T. R., … Lee, R. S. (2009). Multilevel Modeling: A Review of Methodological Issues and Applications. *Review of Educational Research*, 79(1), 69–102. Retrieved from https://doi.org/10.3102/0034654308325581

Demily, C., Rigard, C., Peyroux, E., Chesnoy-Servanin, G., Morel, A., & Franck, N. (2016). «Cognitus & Moi»: A computer-based cognitive remediation program for children with intellectual disability. *Frontiers in Psychiatry*, 7(FEB). Retrieved from https://doi.org/10.3389/fpsyt.2016.00010

Dewulf, D., Noens, I., & Swillen, A. (2013). Adaptieve vaardigheden, cognitief functioneren en gedragsproblemen bij adolescenten met het 22q11.2-deletiesyndroom. *Tijdschrift Voor Psychiatrie*, 55(5), 369–374.

Diamond, A. (2013). Executive Functions. *Annual Reviews of Psychology*, 64, 135–168. Retrieved from https://doi.org/10.1146/annurev-psych-113011-143750

Donohoe, G., Corvin, A., & Robertson, I. H. (2006). Evidence that specific executive functions predict symptom variance among schizophrenia patients with a predominantly negative symptom profile. *Cognitive Neuropsychiatry*, 11(1), 13–32. Retrieved from https://doi.org/10.1080/13546800444000155

Dori, N., Green, T., Weizman, A., & Gothelf, D. (2017). The Effectiveness and Safety of Antipsychotic and Antidepressant Medications in Individuals with 22q11.2 Deletion Syndrome. *Journal of Child and Adolescent Psychopharmacology*, 27(1), 83–90. Retrieved from https://doi.org/10.1089/cap.2014.0075

Drew, L. J., Stark, K. L., Fénelon, K., Karayiorgou, M., Macdermott, A. B., & Gogos, J. A. (2011). Molecular and Cellular Neuroscience Evidence for altered hippocampal function in a mouse model of the human. *Molecular and Cellular Neuroscience*, 47(4), 293–305. Retrieved from https://doi.org/10.1016/j.mcn.2011.05.008

Dubourg, L., Maeder, J., Pouillard, V., Eliez, S., & Schneider, M. (2020). Goal-Directed-Behavior in 22q11.2 Deletion Syndrome: Implication for Social Dysfunctions and the Emergence of Negative Symptoms. *Frontiers in Psychiatry*, 11(April), 1–8. Retrieved from https://doi.org/10.3389/fpsyt.2020.00230

Duijff, S. N., Klaassen, P. W. J., Swanenburg de Veye, H. F. N., Beemer, F. A., Sinnema, G., & Vorstman, J. A. S. (2013). Cognitive and behavioral trajectories in 22q11DS from childhood into adolescence: A prospective 6-year follow-up study. *Research in Developmental Disabilities*, 34(9), 2937–2945. Retrieved from https://doi.org/10.1016/j.ridd.2013.06.001

Duijff, S. N., Klaassen, P. W. J., Swanenburg De Veye, H. F. N., Beemer, F. A., Sinnema, G., & Vorstman, J. A. S. (2012). Cognitive development in children with 22q11.2 deletion syndrome. *British Journal of Psychiatry*, 200(6), 462–468. Retrieved from https://doi.org/10.1192/bjp.bp.111.097139

Dunn, L. M., Theriault-Whalen, L. M., & Dunn, C. M. (1993). *Echelle de Vocabulaire en images de Peabody (EVIP)*. Toronto: Pearson Canada Assessement, Inc.

Eichenbaum, H. (2017). Prefrontal-hippocampal interactions in episodic memory. *Nature Reviews Neuroscience*, 18(9), 547–558. Retrieved from https://doi.org/10.1038/nrn.2017.74

Eichenbaum, H., Yonelinas, A. P., & Ranganath, C. (2007). The Medial Temporal Lobe and Recognition Memory. *Annual Review of Neuroscience*, 30, 123–152. Retrieved from https://doi.org/10.1146/annurev.neuro.30.051606.094328

Eliez, S., Blasey, C. M., Schmitt, E. J., White, C. D., Hu, D., & Reiss, A. L. (2001). Velocardiofacial Syndrome: Are Structural Changes in the Temporal and Mesial Temporal Regions Related to Schizophrenia? *American Journal of Psychiatry*, 158(3), 447–453. Retrieved from https://doi.org/10.1176/appi.ajp.158.3.447

Eliez, S., Schmitt, J. E., White, C. D., & Allan, L. R. (2000). Children and Adolescents With Velocardiofacial Syndrome: A Volumetric MRI Study. *American Journal of Psychiatry*, 157(3), 409–415. Retrieved from https://doi.org/10.1176/appi.ajp.157.3.409

Elliott, G., Isaac, C. L., & Muhlert, N. (2014). Measuring forgetting: A critical review of accelerated long-term forgetting studies. *Cortex*, 54(1), 16–32. Retrieved from https://doi.org/10.1016/j.cortex.2014.02.001

Euston, D. R., Gruber, A. J., & McNaughton, B. L. (2012). The Role of Medial Prefrontal Cortex in Memory and Decision Making. *Neuron*, 76(6), 1057–1070. Retrieved from https://doi.org/10.1016/j.neuron.2012.12.002

Faraone, S. V., Asherson, P., Banaschewski, T., Biederman, J., Buitelaar, J. K., Ramos-Quiroga, J. A., … Franke, B. (2015). Attention-deficit/hyperactivity disorder. *Nature Reviews Disease Primers*, 1. Retrieved from https://doi.org/10.1038/nrdp.2015.20

Faraone, S. V., & Buitelaar, J. (2010). Comparing the efficacy of stimulants for ADHD in

children and adolescents using meta-analysis. *European Child and Adolescent Psychiatry*, 19(4), 353–364. Retrieved from https://doi.org/10.1007/s00787-009-0054-3

Fiksinski, A. M., Breetvelt, E. J., Lee, Y. J., Boot, E., Butcher, N., Palmer, L., … Bassett, A. S. (2019). Neurocognition and adaptive functioning in a genetic high risk model of schizophrenia. *Psychological Medicine*, 49(6), 1047–1054. Retrieved from https://doi.org/10.1017/S0033291718001824

Fioravanti, M., Bianchi, V., & Cinti, M. E. (2012). Cognitive deficits in schizophrenia: An updated metanalysis of the scientific evidence. *BMC Psychiatry*, 12(64), 1–20. Retrieved from https://doi.org/10.1186/1471-244X-12-64

First, M., Spitzer, R., & Williams, J. (1996). *Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I)*. New York: BiometricsResearch, New York State Psychiatric Institute.

Franchini, M, Schaer, M., Glaser, B., Debanné, M., Schneider, M., Menghetti, S., … Eliez, S. (2016). Visual processing of emotional dynamic faces in 22q11 . 2 deletion syndrome. *Journal of Intellectual Disability Research*, 60(4), 308–321. Retrieved from https://doi.org/10.1111/jir.12250

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

Frankland, P. W., & Bontempi, B. (2005). The organization of recent and remote memories. *Nature Reviews Neuroscience*, 6, 119–130. Retrieved from https://doi.org/10.1038/nrn1607

Frankland, P. W., Köhler, S., & Josselyn, S. A. (2013). Hippocampal neurogenesis and forgetting. *Trends in Neurosciences*, 36(9), 497–503. Retrieved from

https://doi.org/10.1016/j.tins.2013.05.002

Freedman, D., & Brown, A. S. (2011). The developmental course of executive functioning in schizophrenia. *International Journal of Developmental Neuroscience*, 29(3), 237–243. Retrieved from https://doi.org/10.1016/j.ijdevneu.2010.11.003

Fung, W. L. A., Butcher, N. J., Costain, G., Andrade, D. M., Boot, E., Chow, E. W. C., … Bassett, A. S. (2015). Practical guidelines for managing adults with 22q11.2 deletion syndrome. *Genetics in Medicine*, 17(8), 599–609. Retrieved from https://doi.org/10.1038/gim.2014.175

Furniss, F., Biswas, A. B., Gumber, R., & Singh, N. (2011). Cognitive phenotype of velocardiofacial syndrome: A review. *Research in Developmental Disabilities*, 32, 2206–2213. Retrieved from https://doi.org/10.1016/j.ridd.2011.05.039

Gioia, G., Isquith, P., Guy, S., & Kenworthy, L. (2000). *Behavior Rating Inventory of Executive Function* (Psychologi). Odessa, FL: Psychological Assessment Ressources.

Glaser, B., Debbané, M., Ottet, M.-C., Vuilleumier, P., Zesiger, P., Antonarakis, S. E., & Eliez, S. (2010). Eye Gaze During Face Processing in Children and Adolescents With 22q11.2 Deletion Syndrome. *Journal of the American Academy of Child & Adolescent Psychiatry*, 49(7), 665–674. Retrieved from https://doi.org/10.1016/j.jaac.2010.04.004

Glaser, B., Lothe, A., Chabloz, M., Dukes, D., Pasca, C., Redoute, J., & Eliez, S. (2012). Candidate Socioemotional Remediation Program for Individuals with Intellectual Disability. *American Journal on Intellectual and Developmental Disabilities*, 117(5), 368–383. Retrieved from https://doi.org/10.1352/1944-7558-117.5.368

Glasson, E. J., Buckley, N., Chen, W., Leonard, H., Epstein, A., Skoss, R., … Downs, J. (2020). Systematic Review and Meta-analysis: Mental Health in Children With Neurogenetic Disorders Associated With Intellectual Disability. *Journal of the American Academy of Child & Adolescent Psychiatry*, 59(9), 1036–1048. Retrieved from

https://doi.org/10.1016/j.jaac.2020.01.006

Gothelf, D., Gruber, R., Presburger, G., Dotan, I., Brand-Gothelf, A., Burg, M., … Weizman, A. (2003). Methylphenidate Treatment for Attention-Deficit/Hyperactivity Disorder in Children and Adolescents With Velocardiofacial Syndrome. *The Journal of Clinical Psychiatry*, 64(10), 1163–1169. Retrieved from https://doi.org/10.4088/jcp.v64n1004

Gothelf, D., Schaer, M., & Eliez, S. (2008). Genes, brain development and psychiatric phenotypes in velo-cardio-facial syndrome. *Developmental Disabilities Research Reviews*, 14(January), 59–68. Retrieved from https://doi.org/10.1002/ddrr.9

Gothelf, D., Schneider, M., Green, T., Debbané, M., Frisch, A., Glaser, B., … Eliez, S. (2013). Risk factors and the evolution of psychosis in 22q11.2 deletion syndrome: A longitudinal 2-site study. *Journal of the American Academy of Child and Adolescent Psychiatry*, 52(11). Retrieved from https://doi.org/10.1016/j.jaac.2013.08.008

Grati, F. R., Gomes, D. M., Carlos, J., Ferreira, P. B., Dupont, C., Alesi, V., … Arsizio, B. (2015). Prevalence of recurrent pathogenic microdeletions and microduplications in over 9500 pregnancies. *Prenatal Diagnosis*, 35, 801–809. Retrieved from https://doi.org/10.1002/pd.4613

Green, T., Gothelf, D., Glaser, B., Debbane, M., Frisch, A., Kotler, M., … Eliez, S. (2009). Psychiatric Disorders and Intellectual Functioning Throughout Development in Velocardiofacial (22q11.2 Deletion) Syndrome. *Journal of the American Academy of Child and Adolescent Psychiatry*, 48(11), 1060–1068. Retrieved from https://doi.org/10.1097/CHI.0b013e3181b76683

Green, T., Weinberger, R., Diamond, A., Ph, D., Berant, M., Hirschfeld, L., … Gothelf, D. (2011). The Effect of Methylphenidate on Prefrontal Cognitive Functioning , Inattention , and Hyperactivity in Velocardiofacial Syndrome. *Journal of Child and Adolescent Psychopharmacology*, 21(6), 589–595. Retrieved from

https://doi.org/10.1089/cap.2011.0042

Guidelines, N. (2018). Attention deficit hyperactivity disorder : diagnosis and management. Retrieved from https://www.nice.org.uk/guidance/ng87/resources/attention-deficit-hyperactivity-disorder-diagnosis-and-management-pdf-1837699732933

Guo, T., Diacou, A., Nomaru, H., McDonald-McGinn, D. M., Hestand, M., Demaerel, W., … Morrow, B. E. (2018). Deletion size analysis of 1680 22q11.2DS subjects identifies a new recombination hotspot on chromosome 22q11.2. *Human Molecular Genetics*, 27(7), 1150–1163. Retrieved from https://doi.org/10.1093/hmg/ddy028

Harrell, W., Eack, S., Hooper, S. R., Keshavan, M. S., Bonner, M. S., Schoch, K., & Shashi, V. (2013). Feasibility and preliminary efficacy data from a computerized cognitive intervention in children with chromosome 22q11.2 deletion syndrome. *Research in Developmental Disabilities*, 34(9), 2606–2613. Retrieved from https://doi.org/10.1016/j.ridd.2013.05.009

Harrell, W., Zou, L., Englander, Z., Hooper, S. R., Keshavan, M. S., Song, A., & Shashi, V. (2017). Frontal Hypoactivation during a Working Memory Task in Children with 22q11 Deletion Syndrome. *Journal of Child Neurology*, 32(1), 94–99. Retrieved from https://doi.org/10.1177/0883073816670813

Henry, J. C., Amelsvoort, T. V., Morris, R. G., Murphy, K. C., Murphy, D. G. M., Owen, M. J., … Murphy, K. C. (2002). An investigation of the neuropsychological profile in velocardiofacial syndrome (VCFS). *Schizophrenia Research*, 40, 471–478. Retrieved from https://doi.org/10.1016/S0920-9964(00)90530-9

Hooper, S. R., Curtiss, K., Schoch, K., Keshavan, M. S., Allen, A., & Shashi, V. (2013). A longitudinal examination of the psychoeducational, neurocognitive, and psychiatric functioning in children with 22q11.2 deletion syndrome. *Research in Developmental Disabilities*, 34(5), 1758–1769. Retrieved from

https://doi.org/10.1016/j.ridd.2012.12.003

Hurks, P. P. M., Schrans, D., Meijs, C., Wassenberg, R., Feron, F. J. M., & Jolles, J. (2010). Developmental changes in semantic verbal fluency: analyses of word productivity as a function of time, clustering, and switching. *Child Neuropsychology*, 16(4), 366–387. Retrieved from https://doi.org/10.1080/09297041003671184

Huss, M., Duhan, P., Gandhi, P., Chen, C.-W., Spannhuth, C., & Kumar, V. (2017). Methylphenidate dose optimization for ADHD treatment: review of safety, efficacy, and clinical necessity. *Neuropsychiatric Disease and Treatment*, Volume 13, 1741–1751. Retrieved from https://doi.org/10.2147/NDT.S130444

Iglesias, J. E., Augustinack, J. C., Nguyen, K., Player, C. M., Player, A., Wright, M., … Van Leemput, K. (2015). A computational atlas of the hippocampal formation using ex vivo, ultra-high resolution MRI: Application to adaptive segmentation of in vivo MRI. *NeuroImage*, 115, 117–137. Retrieved from https://doi.org/10.1016/j.neuroimage.2015.04.042

Insel, T. R. (2010). Rethinking schizophrenia. *Nature*, 468(7321), 187–193. Retrieved from https://doi.org/10.1038/nature09552

Jacobson, C., Shearer, J., Habel, a., Kane, F., Tsakanikos, E., & Kravariti, E. (2010). Core neuropsychological characteristics of children and adolescents with 22q11.2 deletion. *Journal of Intellectual Disability Research*, 54, 701–713. Retrieved from https://doi.org/10.1111/j.1365-2788.2010.01298.x

Jahshan, C. M. S., Heaton, R. K., Golshan, S., & Cadenhead, K. S. (2010). Course of Neurocognitive Deficits in the Prodrome and First Episode of Schizophrenia. *Neuropsychology*, 24(1), 109–120. Retrieved from https://doi.org/10.1037/a0016791.Course

Jalbrzikowski, M., Villalon-Reina, J. E., Karlsgodt, K. H., Senturk, D., Chow, C., Thompson,

P. M., & Bearden, C. E. (2014). Altered white matter microstructure is associated with social cognition and psychotic symptoms in 22q11.2 microdeletion syndrome. *Frontiers in Behavioral Neuroscience*, 8(November), 1–18. Retrieved from https://doi.org/10.3389/fnbeh.2014.00393

Karayiorgou, M., Simon, T. J., & Gogos, J. A. (2010). 22q11.2 microdeletions: Linking DNA structural variation to brain dysfunction and schizophrenia. *Nature Reviews Neuroscience*, 11(6), 402–416. Retrieved from https://doi.org/10.1038/nrn2841

Karr, J. E., Areshenkoff, C. N., Rast, P., Hofer, S. M., Iverson, G. L., & Garcia-Barrera, M. A. (2018). The unity and diversity of executive functions: A systematic review and re-analysis of latent variable studies. *Psychological Bulletin*, 144(11), 1147–1185. Retrieved from https://doi.org/10.1037/bul0000160

Kates, W. R., Krauss, B. R., AbdulSabur, N., Colgan, D., Antshel, K. M., Higgins, A. M., & Shprintzen, R. J. (2007). The neural correlates of non-spatial working memory in velocardiofacial syndrome (22q11.2 deletion syndrome). *Neuropsychologia*, 45(12), 2863–2873. Retrieved from https://doi.org/10.1016/j.neuropsychologia.2007.05.007

Kates, W. R., Mariano, M. A., Antshel, K. M., Chandra, S., Gamble, H., Giordano, M., … Fremont, W. P. (2019). Trajectories of psychiatric diagnoses and medication usage in youth with 22q11.2 deletion syndrome: A 9-year longitudinal study. *Psychological Medicine*, 49(11), 1914–1922. Retrieved from https://doi.org/10.1017/S0033291718002696

Kates, W. R., Miller, A. M., AbdulSabur, N., Antshel, K. M., Conchelos, J., Fremont, W., & Roizen, N. (2006). Temporal lobe anatomy and psychiatric symptoms in velocardiofacial syndrome (22q11.2 deletion syndrome). *Journal of the American Academy of Child and Adolescent Psychiatry*, 45(5), 587–595. Retrieved from https://doi.org/10.1097/01.chi.0000205704.33077.4a

Kaufman, J., Birmaher, B., Brent, D., Rao, U., Flynn, C., Moreci, P., … Ryan, N. (1997). Schedule for affective disorders and schizophrenia for school-age children-present and lifetime version (K-SADS-PL): Initial reliability and validity data. *Journal of the American Academy of Child and Adolescent Psychiatry*, 36(7), 980–988. Retrieved from https://doi.org/10.1097/00004583-199707000-00021

Kay, S., Fiszbein, A., & Opier, L. (1967). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin*, 13, 261–276.

Kennedy, W. P., Mudd, P. A., Maguire, M. A., Souders, M. C., McDonald-McGinn, D. M., Marcus, C. L., … Elden, L. M. (2014). 22q11.2 Deletion syndrome and obstructive sleep apnea. *International Journal of Pediatric Otorhinolaryngology*, 78(8), 1360–1364. Retrieved from https://doi.org/10.1016/j.ijporl.2014.05.031

Lajiness-O'Neill, R. R., Beaulieu, I., Titus, J. B., Asamoah, A., Bigler, E. D., & Pollack, R. (2005). Memory and Learning in Children with 22q11 . 2 Deletion Syndrome : Evidence for Ventral and Dorsal Stream Disruption ? *Child Neuropsychology*, 11, 55–71.

Lepach, A. C., & Petermann, F. (2011). Nonverbal and verbal learning: A comparative study of children and adolescents with 22q11 deletion syndrome, non-syndromal Nonverbal Learning Disorder and memory disorder. *Neurocase*, 17(6), 480–490.

Lewandowski, K. E., Shashi, V., Berry, P. M., & Kwapil, T. R. (2007). Schizophrenic-like neurocognitive deficits in children and adolescents with 22q11 deletion syndrome. *American Journal of Medical Genetics, Part B: Neuropsychiatric Genetics*, 144B(1), 27–36. Retrieved from https://doi.org/10.1002/ajmg.b.30379

Lo-Castro, A., D'Agati, E., & Curatolo, P. (2011). ADHD and genetic syndromes. *Brain and Development*, 33(6), 456–461. Retrieved from https://doi.org/10.1016/j.braindev.2010.05.011

Maeder, J., Sandini, C., Zöller, D., Schneider, M., Bostelmann, M., Pouillard, V., … Eliez, S.

(2020). Long-term verbal memory deficit and associated hippocampal alterations in 22q11.2 deletion syndrome. *Child Neuropsychology*, 26(3), 289–311. Retrieved from https://doi.org/10.1080/09297049.2019.1657392

Maeder, J., Schneider, M., Bostelmann, M., Debbané, M., Glaser, B., Menghetti, S., … Eliez, S. (2016). Developmental trajectories of executive functions in 22q11.2 deletion syndrome. *Journal of Neurodevelopmental Disorders*, 10(8), 1–12. Retrieved from https://doi.org/10.1186/s11689-016-9141-1

Majerus, S., Van der Linden, M., Braissand, V., & Eliez, S. (2007). Verbal Short-Term Memory in Individuals With Chromosome 22q11.2 Deletion: Specific Deficit in Serial Order Retention Capacities? *American Journal on Mental Retardation*, 112(2), 79. Retrieved from https://doi.org/10.1352/0895-8017(2007)112[79:VSMIIW]2.0.CO;2

Mancini, V., Maeder, J., Bortolin, K., Schneider, M., Schaer, M., & Eliez, S. (2020). Combined treatment with SSRI and atypical antipsychotics improves cognition and neurodevelopment in individuals at risk for psychosis.

Mancini, V., Sandini, C., Padula, M. C., Zöller, D., Schneider, M., Schaer, M., & Eliez, S. (2019). Positive psychotic symptoms are associated with divergent developmental trajectories of hippocampal volume during late adolescence in patients with 22q11DS. *Molecular Psychiatry*, d. Retrieved from https://doi.org/10.1038/s41380-019-0443-z

Mancini, V., Zöller, D., Schneider, M., Schaer, M., & Eliez, S. (2020). Abnormal Development and Dysconnectivity of Distinct Thalamic Nuclei in Patients With 22q11.2 Deletion Syndrome Experiencing Auditory Hallucinations. *Biological Psychiatry: Cognitive Neuroscience and Neuroimaging*, 5(9), 875–890. Retrieved from https://doi.org/10.1016/j.bpsc.2020.04.015

Mandler, G. (1980). Recognizing : The Judgment of Previous Occurrence. *Psychological Review*, 87(3), 252–271.

Mariano, M. A., Tang, K., Kurtz, M., & Kates, W. R. (2015). Cognitive remediation for adolescents with 22q11 deletion syndrome (22q11DS): A preliminary study examining effectiveness, feasibility, and fidelity of a hybrid strategy, remote and computer-based intervention. *Schizophrenia Research*, 166(1–3), 283–289. Retrieved from https://doi.org/10.1016/j.schres.2015.05.030

Mariano, M. A., Tang, K., Kurtz, M., & Kates, W. R. (2018). Examining the durability of a hybrid, remote and computer-based cognitive remediation intervention for adolescents with 22q11.2 deletion syndrome. *Early Intervention in Psychiatry*, 12(4), 686–693. Retrieved from https://doi.org/10.1111/eip.12367

Marissal, T., Salazar, R. F., Bertollini, C., Mutel, S., De Roo, M., Rodriguez, I., … Carleton, A. (2018). Restoring wild-type-like CA1 network dynamics and behavior during adulthood in a mouse model of schizophrenia. *Nature Neuroscience*, 21(10), 1412–1420. Retrieved from https://doi.org/10.1038/s41593-018-0225-y

Maynard, T. M., Haskell, G. T., Peters, A. Z., Sikich, L., Lieberman, J. A., & LaMantia, A.-S. (2003). A comprehensive analysis of 22q11 gene expression in the developing and adult brain. *Proceedings of the National Academy of Sciences*, 100(24), 14433–14438. Retrieved from https://doi.org/10.1073/pnas.2235651100

McCabe, K. L., Atkinson, R. J., Cooper, G., Melville, J. L., Harris, J., Schall, U., … Campbell, L. E. (2014). Pre-pulse inhibition and antisaccade performance indicate impaired attention modulation of cognitive inhibition in 22q11 . 2 deletion syndrome (22q11DS). *Journal of Neurodvelopmental Disorders*, 6(38), 1–8.

McCabe, K. L., Rich, D., Loughland, C. M., Schall, U., & Campbell, L. E. (2011). Visual scanpath abnormalities in 22q11.2 deletion syndrome: Is this a face specific deficit? *Psychiatry Research*, 189(2), 292–298. Retrieved from https://doi.org/10.1016/j.psychres.2011.06.012

McDonald-McGinn, D. M., & Sullivan, K. E. (2011). Chromosome 22q11.2 deletion syndrome (DiGeorge syndrome/velocardiofacial syndrome). *Medicine*, 90(1), 1–18. Retrieved from https://doi.org/10.1097/MD.0b013e3182060469

McDonald-McGinn, D. M., Sullivan, K. E., Marino, B., Philip, N., Swillen, A., Vorstman, J. A. S., … Bassett, A. S. (2015). 22q11.2 deletion syndrome. *Nature Reviews Disease Primers*, 1(15071), 1–46. Retrieved from https://doi.org/10.1038/nrdp.2015.71

Mihailov, A., Padula, M. C., Scariati, E., Schaer, M., Schneider, M., & Eliez, S. (2017). Morphological brain changes associated with negative symptoms in patients with 22q11.2 Deletion Syndrome. *Schizophrenia Research*, 188, 52–58. Retrieved from https://doi.org/10.1016/j.schres.2017.01.031

Miller, T. J., McGlashan, T. H., Rosen, J. L., Cadenhead, K., Cannon, T., Ventura, J., … Woods, S. W. (2004). Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: Predictive validity, interrater reliability, and training to reliability. *Schizophrenia Bulletin*, 30(2), 703–716.

Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, A. H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex 'Frontal Lobe' tasks: a latent variable analysis. *Cognitive Psychology*, 41(1), 49–100. Retrieved from https://doi.org/10.1006/cogp.1999.0734

Moberg, P. J., Richman, M. J., Roalf, D. R., Morse, C. L., Graefe, A. C., Brennan, L., … Gur, R. E. (2018). Neurocognitive Functioning in Patients with 22q11.2 Deletion Syndrome: A Meta-Analytic Review. *Behavior Genetics*, 48(4), 259–270. Retrieved from https://doi.org/10.1007/s10519-018-9903-5

Montojo, C. A., Ibrahim, A., Karlsgodt, K. H., Chow, C., Hilton, A. E., Jonas, R. K., … Bearden, C. E. (2014). Disrupted working memory circuitry and psychotic symptoms in 22q11.2 deletion syndrome. *NeuroImage: Clinical*, 4, 392–402. Retrieved from

https://doi.org/10.1016/j.nicl.2014.01.010

Morrison, S., Chawner, S. J. R. A., van Amelsvoort, T. A. M. J., Swillen, A., Vingerhoets, C., Vergaelen, E., … van den Bree, M. B. M. (2020). Cognitive deficits in childhood, adolescence and adulthood in 22q11.2 deletion syndrome and association with psychopathology. *Translational Psychiatry*, 10(1). Retrieved from https://doi.org/10.1038/s41398-020-0736-7

Mosheva, M., Pouillard, V., Fishman, Y., Dubourg, L., Sofrin-frumer, D., Serur, Y., … Schneider, M. (2018). Education and employment trajectories from childhood to adulthood in individuals with 22q11.2 deletion syndrome. *European Child and Adolescent Psychiatryild & Adolescent Psychiatry*, 28(1), 31–42. Retrieved from https://doi.org/10.1007/s00787-018-1184-2

Moulding, H. A., Bartsch, U., Hall, J., Jones, M. W., Linden, D. E., Owen, M. J., & van den Bree, M. B. M. (2020). Sleep problems and associations with psychopathology and cognition in young people with 22q11.2 deletion syndrome (22q11.2DS). *Psychological Medicine*, 50(7), 1191–1202. Retrieved from https://doi.org/10.1017/S0033291719001119

Mukherjee, A., Carvalho, F., Eliez, S., & Caroni, P. (2019). Long-Lasting Rescue of Network and Cognitive Dysfunction in a Genetic Schizophrenia Model. *Cell*, 178(6), 1387-1402.e14. Retrieved from https://doi.org/10.1016/j.cell.2019.07.023

Murphy, K. C., Jones, L. a, & Owen, M. J. (1999). High rates of schizophrenia in adults with velo-cardio-facial syndrome. *Archives of General Psychiatry*, 56, 940–945. Retrieved from https://doi.org/10.1016/S0920-9964(00)90364-5

Mutlu, A. K., Schneider, M., Debbané, M., Badoud, D., Eliez, S., & Schaer, M. (2013). Sex differences in thickness, and folding developments throughout the cortex. *NeuroImage*, 82, 200–7. Retrieved 10 February 2015 from

https://doi.org/10.1016/j.neuroimage.2013.05.076

Nakahara, S., Matsumoto, M., & van Erp, T. G. M. (2018). Hippocampal subregion abnormalities in schizophrenia: A systematic review of structural and physiological imaging studies. *Neuropsychopharmacology Reports*, 38(4), 156–166. Retrieved from https://doi.org/10.1002/npr2.12031

Niarchou, M., Martin, J., Thapar, A., Owen, M. J., & van den Bree, M. B. M. (2015). The clinical presentation of attention deficit-hyperactivity disorder (ADHD) in children with 22q11.2 deletion syndrome. *American Journal of Medical Genetics Part B: Neuropsychiatric Genetics*, 168(8), 730–738. Retrieved from https://doi.org/10.1002/ajmg.b.32378

Niarchou, M., Zammit, S., van Goozen, S. H. M., Thapar, A., Tierling, H. M., Owen, M. J., & Van Den Bree, M. B. M. (2014). Psychopathology and cognition in children with 22q11.2 deletion syndrome. *British Journal of Psychiatry*, 204(1), 46–54. Retrieved from https://doi.org/10.1192/bjp.bp.113.132324

Nigg, J. T. (2005). Neuropsychologic theory and findings in attention-deficit/hyperactivity disorder: The state of the field and salient challenges for the coming decade. *Biological Psychiatry*, 57(11), 1424–1435. Retrieved from https://doi.org/10.1016/j.biopsych.2004.11.011

Olsen, L., Sparsø, T., Weinsheimer, S. M., Dos Santos, M. B. Q., Mazin, W., Rosengren, A., … Werge, T. (2018). Prevalence of rearrangements in the 22q11.2 region and population-based risk of neuropsychiatric and developmental disorders in a Danish population: a case-cohort study. *The Lancet Psychiatry*, 5(7), 573–580. Retrieved from https://doi.org/10.1016/S2215-0366(18)30168-8

Oskarsdóttir, S., Vujic, M., & Fasth, a. (2004). Incidence and prevalence of the 22q11 deletion syndrome: a population-based study in Western Sweden. *Archives of Disease in*

Childhood, 89, 148–151. Retrieved from https://doi.org/10.1136/adc.2003.026880

Overall, J. E., & Gorham, D. (1962). The Brief Psychiatric Rating Scale. *Psychological Reports*, 10, 799–812.

Owens, S. F., Picchioni, M. M., Rijsdijk, F. V., Stahl, D., Vassos, E., Rodger, A. K., … Toulopoulou, T. (2011). Genetic overlap between episodic memory deficits and schizophrenia: Results from the Maudsley Twin Study. *Psychological Medicine*, 41(3), 521–532. Retrieved from https://doi.org/10.1017/S0033291710000942

Padula, M. C., Scariati, E., Schaer, M., & Eliez, S. (2018). A mini review on the contribution of the anterior cingulate cortex in the risk of psychosis in 22q11.2 deletion syndrome. *Frontiers in Psychiatry*, 9(AUG), 9–14. Retrieved from https://doi.org/10.3389/fpsyt.2018.00372

Padula, M. C., Schaer, M., Scariati, E., Maeder, J., Schneider, M., & Eliez, S. (2017). Multimodal investigation of triple network connectivity in patients with 22q11ds and association with executive functions. *Human Brain Mapping*, 38(4), 2177–2189. Retrieved from https://doi.org/10.1002/hbm.23512

Padula, M. C., Schaer, M., Scariati, E., Mutlu, A. K., Zöller, D., Schneider, M., & Eliez, S. (2017). Quantifying indices of short- and long-range white matter connectivity at each cortical vertex. *PLoS ONE*, 12(11), 1–20. Retrieved from https://doi.org/10.1371/journal.pone.0187493

Padula, M. C., Schaer, M., Scariati, E., Schneider, M., Van De Ville, D., Debbané, M., & Eliez, S. (2015). Structural and functional connectivity in the default mode network in 22q11.2 deletion syndrome. *Journal of Neurodevelopmental Disorders*, 7(1), 1–13. Retrieved from https://doi.org/10.1186/s11689-015-9120-y

Peng, H., & Lu, Y. (2012). Model selection in linear mixed effect models. *Journal of Multivariate Analysis*, 109, 109–129. Retrieved from

https://doi.org/10.1016/j.jmva.2012.02.005

Philip, N., & Bassett, A. (2011). Cognitive, behavioural and psychiatric phenotype in 22q11.2 deletion syndrome. *Behavior Genetics*, 41, 403–412. Retrieved from https://doi.org/10.1007/s10519-011-9468-z

Picard, L., Cousin, S., Guillery-Girard, B., Eustache, F., & Piolino, P. (2012). How Do the Different Components of Episodic Memory Develop? Role of Executive Functions and Short-Term Feature-Binding Abilities. *Child Development*, 83(3), 1037–1050. Retrieved from https://doi.org/10.1111/j.1467-8624.2012.01736.x

Piccini, G., Menghini, D., D'Andrea, A., Caciolo, C., Pontillo, M., Armando, M., … Alfieri, P. (2017). Visual perception skills: a comparison between patients with Noonan syndrome and 22q11.2 deletion syndrome. *Genes, Brain and Behavior*, 16(6), 627–634. Retrieved from https://doi.org/10.1111/gbb.12381

Preston, A. R., & Eichenbaum, H. (2013). Interplay of hippocampus and prefrontal cortex in memory. *Current Biology*, 23(17), R764–R773. Retrieved from https://doi.org/10.1016/j.cub.2013.05.041

Quintero, A. I., Beaton, E. A., Harvey, D. J., Ross, J. L., & Simon, T. J. (2014). Common and specific impairments in attention functioning in girls with chromosome 22q11.2 deletion, fragile X or Turner syndromes. *Journal of Neurodevelopmental Disorders*, 6(1), 1–15. Retrieved from https://doi.org/10.1186/1866-1955-6-5

Ramanathan, S., Mattiaccio, L. M., Coman, I. L., Botti, J. C., Fremont, W., Faraone, S. V, … Kates, W. R. (2017). Longitudinal trajectories of cortical thickness as a biomarker for psychosis in individuals with 22q11.2 deletion syndrome. *Schizophrenia Research*, 188, 35–41. Retrieved from https://doi.org/10.1016/j.schres.2016.11.041

Rees, E., Walters, J. T. R., Georgieva, L., Isles, A. R., Chambert, K. D., Richards, A. L., … Kirov, G. (2014). Analysis of copy number variations at 15 schizophrenia-associated

loci. *British Journal of Psychiatry*, 204(2), 108–114. Retrieved from https://doi.org/10.1192/bjp.bp.113.131052

Reich, W. (2000). Diagnostic interview for children and adolescents (DICA). *Journal of the American Academy of Child and Adolescent Psychiatry*, 39(1), 59–66. Retrieved from https://doi.org/10.1097/00004583-200001000-00017

Reichenberg, A., Caspi, A., Harrington, H., Houts, R., Keefe, R. S. E., Murray, R. M., … Moffitt, T. E. (2010). Static and dynamic cognitive deficits in childhood preceding adult schizophrenia: A 30-year study. *American Journal of Psychiatry*, 167(2), 160–169. Retrieved from http://ajp.psychiatryonline.org/cgi/reprint/167/2/160%5Cnhttp://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed12&NEWS=N&AN=358226706

Reilly, C. (2012). Behavioural phenotypes and special educational needs: Is aetiology important in the classroom? *Journal of Intellectual Disability Research*, 56(10), 929–946. Retrieved from https://doi.org/10.1111/j.1365-2788.2012.01542.x

Reilly, C., Senior, J., & Murtagh, L. (2015). ASD, ADHD, mental health conditions and psychopharmacology in neurogenetic syndromes: Parent survey. *Journal of Intellectual Disability Research*, 59(4), 307–318. Retrieved from https://doi.org/10.1111/jir.12147

Reilly, C., & Stedman, L. (2013). Supporting children with genetic syndromes in the classroom: The example of 22q deletion syndrome. *Support for Learning*, 28(3), 115–121. Retrieved from https://doi.org/10.1111/1467-9604.12029

Resch, C., Martens, R., & Hurks, P. (2014). Analysis of young children's abilities to cluster and switch during a verbal fluency task. *The Clinical Neuropsychologist*, 28(8), 1295–1310. Retrieved from https://doi.org/10.1080/13854046.2014.978382

Rey, A. (1958). *L'examen clinique en psychologie*. Paris: Presse Universitaire de France, PUF.

Ritter, B. C., Perrig, W., Steinlin, M., & Everts, R. (2014). Cognitive and behavioral aspects of executive functions in children born very preterm. *Child Neuropsychology*, 20(2), 129–144. Retrieved from https://doi.org/10.1080/09297049.2013.773968

Robin, N. H., & Shprintzen, R. J. (2005). Defining the Clinical Spectrum of Deletion 22q11.2. *The Journal of Pediatrics*, 147(1), 90–96. Retrieved from https://doi.org/10.1016/j.jpeds.2005.03.007

Roediger, H. L., & Butler, A. C. (2011). The critical role of retrieval practice in long-term retention. *Trends in Cognitive Sciences*, 15(1), 20–27. Retrieved from https://doi.org/10.1016/j.tics.2010.09.003

Rogdaki, M., Gudbrandsen, M., McCutcheon, R. A., Blackmore, C. E., Brugger, S., Ecker, C., … Howes, O. (2020). Magnitude and heterogeneity of brain structural abnormalities in 22q11.2 deletion syndrome: a meta-analysis. *Molecular Psychiatry*. Retrieved from https://doi.org/10.1038/s41380-019-0638-3

Romine, C. B., & Reynolds, C. R. (2005). A model of the development of frontal lobe functioning: Findings from a meta-analysis. *Applied Neuropsychology*, 12(4), 190–201. Retrieved from https://doi.org/10.1207/s15324826an1204_2

Roth, R. M., Isquith, P. K., & Gioia, G. A. (2002). *Behavior Rating Inventory of Executive Function - Adult (BRIEF-A)*. Odessa, FL: Psychological Assessment Ressources.

Ryan, A. K., Goodship, J. A., Wilson, D. I., Philip, N., Levy, A., Seidel, H., … Scambler, P. J. (1997). Spectrum of clinical features associated with interstitial chromosome 22q11 deletions: A European collaborative study. *Journal of Medical Genetics*, 34(10), 798–804. Retrieved from https://doi.org/10.1136/jmg.34.10.798

Sandini, C., Scariati, E., Padula, M. C., Schneider, M., Schaer, M., Van De Ville, D., & Eliez, S. (2018). Cortical Dysconnectivity Measured by Structural Covariance Is Associated With the Presence of Psychotic Symptoms in 22q11.2 Deletion Syndrome. *Biological*

Psychiatry: Cognitive Neuroscience and Neuroimaging, 3(5), 433–442. Retrieved from https://doi.org/10.1016/j.bpsc.2017.04.008

Sauzéon, H., Lestage, P., Raboutet, C., N'Kaoua, B., & Claverie, B. (2004). Verbal fluency output in children aged 7-16 as a function of the production criterion: Qualitative analysis of clustering, switching processes, and semantic network exploitation. *Brain and Language*, 89(1), 192–202. Retrieved from https://doi.org/10.1016/S0093-934X(03)00367-5

Scariati, E., Padula, M. C., Schaer, M., & Eliez, S. (2016). Long-range dysconnectivity in frontal and midline structures is associated to psychosis in 22q11.2 deletion syndrome. *Journal of Neural Transmission*, 123(8), 823–839. Retrieved from https://doi.org/10.1007/s00702-016-1548-z

Scariati, E., Schaer, M., Richiardi, J., Schneider, M., Debbané, M., Van De Ville, D., & Eliez, S. (2014). Identifying 22q11.2 Deletion Syndrome and Psychosis Using Resting-State Connectivity Patterns. *Brain Topography*, 27(6), 808–821. Retrieved from https://doi.org/10.1007/s10548-014-0356-8

Scarpazza, C., Lattanzi, G. M., Antoniades, M., Di Fabio, F., Sartori, G., Eickhoff, S. B., … Tognin, S. (2019). Systematic review and multi-modal meta-analysis of magnetic resonance imaging findings in 22q11.2 deletion syndrome: Is more evidence needed? *Neuroscience and Biobehavioral Reviews*, 107(September), 143–153. Retrieved from https://doi.org/10.1016/j.neubiorev.2019.09.004

Schaer, M., Debbané, M., Bach Cuadra, M., Ottet, M. C., Glaser, B., Thiran, J. P., & Eliez, S. (2009). Deviant trajectories of cortical maturation in 22q11.2 deletion syndrome (22q11DS): A cross-sectional and longitudinal study. *Schizophrenia Research*, 115(2–3), 182–190. Retrieved from https://doi.org/10.1016/j.schres.2009.09.016

Schneider, M., Debbané, M., Bassett, A. S., Chow, E. W. C., Fung, W. L. A., Bree, M. B. M.

van den, … Eliez, S. (2014). Psychiatric disorders from childhood to adulthood in 22q11.2 deletion syndrome: results from the international consortium on brain and behavior in 22q11.2 deletion syndrome. *American Journal of Psychiatry*, 171(6), 627–639. Retrieved from https://doi.org/10.1016/j.biotechadv.2011.08.021.Secreted

Schneider, M., Eliez, S., Birr, J., Menghetti, S., Debbané, M., & Van Der Linden, M. (2016). Multitasking abilities in adolescents with 22q11.2 deletion syndrome: Results from an experimental ecological paradigm. *American Journal on Intellectual and Developmental Disabilities*, 121(2), 151–164. Retrieved from https://doi.org/10.1352/1944-7558-121.2.151

Schneider, M., Schaer, M., Mutlu, A. K., Menghetti, S., Glaser, B., Debbané, M., & Eliez, S. (2014). Clinical and cognitive risk factors for psychotic symptoms in 22q11.2 deletion syndrome: A transversal and longitudinal approach. *European Child and Adolescent Psychiatry*, 23(6), 425–436. Retrieved from https://doi.org/10.1007/s00787-013-0469-8

Schneider, M., Van der Linden, M., Menghetti, S., Glaser, B., Debbané, M., & Eliez, S. (2014). Predominant negative symptoms in 22q11.2 deletion syndrome and their associations with cognitive functioning and functional outcome. *Journal of Psychiatric Research*, 48(1), 86–93. Retrieved from https://doi.org/10.1016/j.jpsychires.2013.10.010

Scott, J. A., Goodrich-Hunsaker, N., Kalish, K., Lee, A., Hunsaker, M. R., Schumann, C. M., … Simon, T. J. (2016). The hippocampi of children with chromosome 22q11.2 deletion syndrome have localized anterior alterations that predict severity of anxiety. *Journal of Psychiatry and Neuroscience*, 41(3), 203–213. Retrieved from https://doi.org/10.1503/jpn.140299

Semkovska, M., Bédard, M. A., Godbout, L., Limoge, F., & Stip, E. (2004). Assessment of executive dysfunction during activities of daily living in schizophrenia. *Schizophrenia Research*, 69(2–3), 289–300. Retrieved from

https://doi.org/10.1016/j.schres.2003.07.005

Sevino, O. (1998). *Les fonctions exécutives chez l'enfant : développement, structure et évaluation*. University of Geneva.

Shapiro, H. M., Tassone, F., Choudhary, N. S., & Simon, T. J. (2014). The development of cognitive control in children with chromosome 22q11.2 deletion syndrome. *Frontiers in Psychology*, 5(June), 1–14. Retrieved from https://doi.org/10.3389/fpsyg.2014.00566

Shapiro, H. M., Wong, L. M., & Simon, T. J. (2013). A cross-sectional analysis of the development of response inhibition in children with chromosome 22q11.2 deletion syndrome. *Frontiers in Psychiatry*, 4(AUG), 1–10. Retrieved from https://doi.org/10.3389/fpsyt.2013.00081

Shashi, V., Kwapil, T. R., Kaczorowski, J., Berry, M. N., Santos, C. S., Howard, T. D., … Keshavan, M. S. (2010). Evidence of gray matter reduction and dysfunction in chromosome 22q11.2 deletion syndrome. *Psychiatry Research - Neuroimaging*, 181(1), 1–8. Retrieved from https://doi.org/10.1016/j.pscychresns.2009.07.003

Shaw, P., Gogtay, N., & Rapoport, J. (2010). Childhood psychiatric disorders as anomalies in neurodevelopmental trajectories. *Human Brain Mapping*, 31(6), 917–925. Retrieved from https://doi.org/10.1002/hbm.21028

Shprintzen, R. J. (2008). Velo-Cardio-Facial Syndrome: 30 Years of Study. *Developmental Disabilies Research Reviews*, 14(1), 3–10. Retrieved from https://doi.org/10.1002/ddrr.2.Velo-Cardio-Facial

Sigurdsson, T., Stark, K. L., Karayiorgou, M., Gogos, J. A., & Gordon, J. A. (2010). Impaired hippocampal-prefrontal synchrony in a genetic mouse model of schizophrenia. *Nature*, 464(7289), 763–767. Retrieved from https://doi.org/10.1038/nature08855

Simon, T. J., Ding, L., Bish, J. P., McDonald-McGinn, D. M., Zackai, E. H., & Gee, J. (2005). Volumetric, connective, and morphologic changes in the brains of children with

chromosome 22q11.2 deletion syndrome: An integrative study. *NeuroImage*, 25(1), 169–180. Retrieved from https://doi.org/10.1016/j.neuroimage.2004.11.018

Sinderberry, B., Brown, S., Hammond, P., Stevens, A. F., Schall, U., Murphy, D. G. M., … Campbell, L. E. (2013). Subtypes in 22q11.2 deletion syndrome associated with behaviour and neurofacial morphology. *Research in Developmental Disabilities*, 34(1), 116–125. Retrieved from https://doi.org/10.1016/j.ridd.2012.07.025

Sousa, S. S., Amaro, E., Crego, A., Gonçalves, Ó. F., & Sampaio, A. (2018). Developmental trajectory of the prefrontal cortex: a systematic review of diffusion tensor imaging studies. *Brain Imaging and Behavior*, 12(4), 1197–1210. Retrieved from https://doi.org/10.1007/s11682-017-9761-4

Sparrow, S. S. (2011). Vineland Adaptive Behavior Scales. In *Encyclopedia of Clinical Neuropsychology* (pp. 2618–2621). New York, NY: Springer New York. Retrieved from https://doi.org/10.1007/978-0-387-79948-3_1602

Squarcione, C., Torti, M. C., Di Fabio, F., & Biondi, M. (2013). 22q11 deletion syndrome: a review of the neuropsychiatric features and their neurobiological basis. *Neuropsychiatric Disease and Treatment*, 9, 1873–1884. Retrieved from https://doi.org/10.2147/NDT.S52188

Squire, L. R., & Alvarez, P. (1995). Reterograde amnesia and memory consolidation: a neurobiological persepctive. *Current Opinion in Neurobiology*, 5(2), 169–177.

Squire, L. R., Stark, C. E. L., & Clark, R. E. (2004). The Medial Temporal Lobe. *Annual Review of Neuroscience*, 27, 279–306. Retrieved from https://doi.org/10.1146/annurev.neuro.27.070203.144130

Squire, L. R., & Zola-Morgan, S. (1991). Medial temporal lobe memory system. *Science*, 253, 1380–1386.

Stoddard, J., Beckett, L., & Simon, T. J. (2011). Atypical development of the executive

attention network in children with chromosome 22q11.2 deletion syndrome. *Journal of Neurodevelopmental Disorders*, 3(1), 76–85. Retrieved from https://doi.org/10.1007/s11689-010-9070-3

Sun, D., Ching, C. R. K., Lin, A., Forsyth, J. K., Kushan, L., Vajdi, A., … Bearden, C. E. (2018). Large-scale mapping of cortical alterations in 22q11.2 deletion syndrome: Convergence with idiopathic psychosis and effects of deletion size. *Molecular Psychiatry*, 1–13. Retrieved from https://doi.org/10.1038/s41380-018-0078-5

Sundram, F., Campbell, L. E., Azuma, R., Daly, E., Bloemen, O. J. N., Barker, G. J., … Murphy, D. G. M. (2010). White matter microstructure in 22q11 deletion syndrome: A pilot diffusion tensor imaging and voxel-based morphometry study of children and adolescents. *Journal of Neurodevelopmental Disorders*, 2(2), 77–92. Retrieved from https://doi.org/10.1007/s11689-010-9043-6

Swanson, J., Baler, R. D., & Volkow, N. D. (2011). Understanding the effects of stimulant medications on cognition in individuals with attention-deficit hyperactivity disorder: A decade of progress. *Neuropsychopharmacology*, 36(1), 207–226. Retrieved from https://doi.org/10.1038/npp.2010.160

Swillen, A. (2016). The importance of understanding cognitive trajectories: The case of 22q11.2 deletion syndrome. *Current Opinion in Psychiatry*, 29(2), 133–137. Retrieved from https://doi.org/10.1097/YCO.0000000000000231

Swillen, A., & McDonald-McGinn, D. (2015). Developmental Trajectories in 22q11.2 Deletion. *American Journal of Medical Genetics Part C*, 169C, 172–181. Retrieved from https://doi.org/10.1002/ajmg.c.31435

Tang, S. X., Yi, J. J., Calkins, M. E., Whinna, D. A., Kohler, C. G., Souders, M. C., … Gur, R. E. (2014). Psychiatric disorders in 22q11.2 deletion syndrome are prevalent but undertreated. *Psychological Medicine*, 44(6), 1267–1277. Retrieved from

https://doi.org/10.1017/S0033291713001669

Taş Torun, Y., Işik Taner, Y., Güney, E., & İseri, E. (2020). Osmotic Release Oral System-Methylphenidate Hydrochloride (OROS-MPH) versus atomoxetine on executive function improvement and clinical effectiveness in ADHD: A randomized controlled trial. *Applied Neuropsychology: Child*. Retrieved from https://doi.org/10.1080/21622965.2020.1796667

Taylor, L. E., Kates, W. R., Fremont, W., & Antshel, K. M. (2018). Young adult outcomes for children With 22q11 deletion syndrome and comorbid ADHD. *Journal of Pediatric Psychology*, 43(6), 636–644. Retrieved from https://doi.org/10.1093/jpepsy/jsy002

Thissen, D., Steinberg, L., & Kuang, D. (2002). Quick and Easy Implementation of the Benjamini-Hochberg Procedure for Controlling the False Positive Rate in Multiple Comparisons. *Journal of Educational and Behavioral Statistics*, 27(1), 77–83. Retrieved from https://doi.org/10.3102/10769986027001077

Thomson, D. M., & Tulving, E. (1973). Encoding specificity and retrieval processes in episodic memory. *Psychological Review*, 80(5), 352–373. Retrieved from http://gureckislab.org/courses/fall15/lhc/readings/TulvingThompson1973.pdf

Tomescu, M. I., Rihs, T. A., Becker, R., Britz, J., Custo, A., Grouiller, F., … Michel, C. M. (2014). Deviant dynamics of EEG resting state pattern in 22q11.2 deletion syndrome adolescents: A vulnerability marker of schizophrenia? *Schizophrenia Research*, 157(1–3), 175–181. Retrieved from https://doi.org/10.1016/j.schres.2014.05.036

Turgay, A., Ginsberg, L., Sarkis, E., Jain, R., Adeyi, B., Gao, J., … Findling, R. L. (2010). Executive function deficits in children with attention-deficit/ hyperactivity disorder and improvement with lisdexamfetamine dimesylate in an open-label study. *Journal of Child and Adolescent Psychopharmacology*, 20(6), 503–511. Retrieved from https://doi.org/10.1089/cap.2009.0110

Twisk, J., & Hoekstra, T. (2012). Classifying developmental trajectories over time should be done with great caution: A comparison between methods. *Journal of Clinical Epidemiology*, 65(10), 1078–1087. Retrieved from https://doi.org/10.1016/j.jclinepi.2012.04.010

Tyburski, E., Sokołowski, A., Chęć, M., Pełka-Wysiecka, J., & Samochowiec, A. (2015). Neuropsychological Characteristics of Verbal and Non-Verbal Fluency in Schizophrenia Patients. *Archives of Psychiatric Nursing*, 29, 33–38. Retrieved from https://doi.org/10.1016/j.apnu.2014.09.009

Valli, I., Tognin, S., Fusar-Poli, P., & Mechelli, A. (2012). Episodic Memory Dysfunction in Individuals at High-Risk of Psychosis: A Systematic Review of Neuropsychological and Neurofunctional Studies. *Current Pharmaceutical Design*, 18(4), 443–458. Retrieved from https://doi.org/10.2174/138161212799316271

Vargas, T., Dean, D. J., Osborne, K. J., Gupta, T., Ristanovic, I., Ozturk, S., … Mittal, V. A. (2018). Hippocampal subregions across the psychosis spectrum. *Schizophrenia Bulletin*, 44(5), 1091–1099. Retrieved from https://doi.org/10.1093/schbul/sbx160

Vorstman, J. A. S., Breetvelt, E. J., Duijff, S. N., Eliez, S., Schneider, M., Jalbrzikowski, M., … Bassett, A. S. (2015). Cognitive Decline Preceding the Onset of Psychosis in Patients With 22q11.2 Deletion Syndrome. *JAMA Psychiatry*, 72(4), 377. Retrieved from https://doi.org/10.1001/jamapsychiatry.2014.2671

Waber, D. P., De Moor, C., Forbes, P. W., Almli, C. R., Botteron, K. N., Leonarf, G., … Rumsey, J. (2007). The NIH MRI study of normal brain development: Performance of a population based sample of healthy children aged 6 to 18 years on a neuropsychological battery. *Journal of the International Neuropsychological Society*, 13(5), 729–746. Retrieved from https://doi.org/10.1017/S1355617707070841

Wechsler, D. (1991). *The Wechsler Intelligence Scale for Children - third edition*. San

Antonio, TX: The Psychological Corporation.

Wechsler, D. (1997a). *Wechsler Adult Intelligence Scale - third edition*. San Antonio, TX: The Psychological Corporation.

Wechsler, D. (1997b). *Wechsler Memory Scale (Third Ed.)*. San Antonio, TX: Psychological Corporation.

Wechsler, D. (2004). *The Wechsler intelligence scale for children - fourth edition*. London: Pearson Assessment.

Wechsler, D. (2010). *Wechsler Memory Scale, fourth edition*. San Antonio, TX: Psychological Corporation.

Wechsler, D. (2011). *Wechsler Adult Intelligence Scale-IV: administration and scoring manual*. San Antonio: Psychological Corporation.

Wechsler, D. (2016). *Wechsler intelligence scale for children - fifth edition*. London: Pearson Assessment.

Weinberger, R., Yi, J., Calkins, M., Guri, Y., McDonald-McGinn, D. M., Emanuel, B. S., … Gothelf, D. (2016). Neurocognitive profile in psychotic versus nonpsychotic individuals with 22q11.2 deletion syndrome. *European Neuropsychopharmacology*, 26(10), 1610–1618. Retrieved from https://doi.org/10.1016/j.euroneuro.2016.08.003

Wilhelm, I., Prehn-Kristensen, A., & Born, J. (2012). Sleep-dependent memory consolidation - What can be learnt from children? *Neuroscience and Biobehavioral Reviews*, 36(7), 1718–1728. Retrieved from https://doi.org/10.1016/j.neubiorev.2012.03.002

Willcutt, E. G. (2012). The Prevalence of DSM-IV Attention-Deficit/Hyperactivity Disorder: A Meta-Analytic Review. *Neurotherapeutics*, 9(3), 490–499. Retrieved from https://doi.org/10.1007/s13311-012-0135-8

Willcutt, E. G., Doyle, A. E., Nigg, J. T., Faraone, S. V., & Pennington, B. F. (2005). Validity of the executive function theory of attention-deficit/ hyperactivity disorder: A meta-

analytic review. *Biological Psychiatry*, 57(11), 1336–1346. Retrieved from https://doi.org/10.1016/j.biopsych.2005.02.006

Williams, J., Rickert, V., Hogan, J., Zolten, A. J., Satz, P., D'Elia, L. F., … Light, R. (1995). Children's color trails. *Archives of Clinical Neuropsychology*, 10(3), 211–223. Retrieved from https://doi.org/10.1016/0887-6177(94)00041-N

Woodin, M., Wang, P. P., Aleman, D., McDonald-McGinn, D., Zackai, E., & Moss, E. (2001). Neuropsychological profile of children and adolescents with the 22q11.2 microdeletion. *Genetics in Medicine*, 3(1), 34–39. Retrieved from https://doi.org/10.1097/00125817-200101000-00008

Yang, L., Cao, Q., Shuai, L., Li, H., Chan, R. C. K., & Wang, Y. (2012). Comparative study of OROS-MPH and atomoxetine on executive function improvement in ADHD: A randomized controlled trial. *International Journal of Neuropsychopharmacology*, 15(1), 15–26. Retrieved from https://doi.org/10.1017/S1461145711001490

Yi, J. J., Calkins, M. E., Tang, S. X., Kohler, C. G., McDonald-McGinn, D. M., Zackai, E. H., … Gur, R. E. (2015). Impact of Psychiatric Comorbidity and Cognitive Deficit on Function in 22q11.2 Deletion Syndrome. *The Journal of Clinical Psychiatry*, 76(10), e1262–e1270. Retrieved from https://doi.org/10.4088/JCP.14m09197

Young, A. S., Shashi, V., Schoch, K., Kwapil, T., & Hooper, S. R. (2011). Discordance in diagnoses and treatment of psychiatric disorders in children and adolescents with 22q11.2 deletion syndrome. *Asian Journal of Psychiatry*, 4(2), 119–124. Retrieved from https://doi.org/10.1016/j.ajp.2011.03.002

Zarchi, O., Diamond, a., Weinberger, R., Abbott, D., Carmel, M., Frisch, a., … Gothelf, D. (2014). A comparative study of the neuropsychiatric and neurocognitive phenotype in two microdeletion syndromes: Velocardiofacial (22q11.2 deletion) and Williams (7q11.23 deletion) syndromes. *European Psychiatry*, 29(4), 203–210. Retrieved from

https://doi.org/10.1016/j.eurpsy.2013.07.001

Zinkstok, J., & Van Amelsvoort, T. (2005). Neuropsychological profile and neuroimaging in patients with 22q11.2 Deletion Syndrome: A review. *Child Neuropsychology*, 11(1), 21–37. Retrieved from https://doi.org/10.1080/09297040590911194