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UNIVERSITÉ DE GENÈVE

FACULTY OF PSYCHOLOGY AND EDUCATIONAL SCIENCES

Melodie Derome

Sous la direction du Professeur Martin Debbané

Schizotypy, the brain, and strange face illusions in the mirror

Trait-State approach & neurodevelopmental correlates

THESE

Présentée à la

Faculté de psychologie et des sciences de l'éducation

De l'Université de Genève

Pour l'obtention du grade de Docteure en Psychologie

Par

Mélodie DEROME

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Schizotypy, the brain, and strange face illusions in the mirror

Mélodie Derome

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for the Degree of PhD in Psychology

Geneva University

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Abstract

This thesis, which finds itself within the field of clinical psychology, reunites the concept of schizotypy with the dimension of self, using a trait-state approach. According to phenomenologists, the dimension of self is at the core of the psychosis continuum, although absent from the definition of schizotypy in psychiatric classifications. This project investigates the concept of schizotypy and its link with anomalous self-experiences (ASEs), as well as their neurobiological underpinnings in the general population. Schizotypy constitutes a personality trait, distributed in the general population, which in its extreme expression can be considered as a personality-based risk factor for the development of psychosis. On the other hand, experiential anomalies of the self are expressed in terms of subtle phenomena observable at non-clinical levels in healthy individuals, as well as along the psychosis of clinical severity. Numerous studies have shown that ASEs are more frequent in individuals who develop disorders along the psychosis spectrum and within this project they will be experimentally induced to reproduce a state that resembles clinical symptoms observed in high-risk states. That is why the study, in the general population, of these two developing factors, as well as their potential interaction, can help further understand the emerging risk of psychosis. This project contributes to the growing field of research interested in early detection. The longitudinal dimension and the multimodal methodological approach provide additional opportunities to circumscribe these phenomena in non-ill, developing individuals, and assess key interindividual variations leading to risk. The final goals of this research are to study the relationships between schizotypy and experimentally induced self-anomalies; to chart their associations with cerebral structure and function, using both cross-sectional and longitudinal design; and to critically inform research on the emerging risk of psychosis. Throughout this project, we will use a specific task to experimentally induce ASEs, the mirror gazing task (MGT), and we will employ the Schizotypal Personality Questionnaire to chart the

development of schizotypy. The studies are divided in three steps, yielding a total of five studies. The first two studies investigate developmental trajectories of cortical thickness and subcortical structures' volumes in relation to the different dimensions of schizotypy throughout adolescence. While the third behavioral study aims at further characterizing and defining experimentally induced ASEs and their specificities according to age in the context of the MGT. The fourth study then leads us to develop a functional fMRI MGT task in order to explore the neural activation patterns preceding, ongoing and following apparitions of ASEs-like phenomena. Whereas in the ultimate study, we examine the relationship between schizotypy, experimentally induced ASEs and resting-state networks, using both a cross-sectional and longitudinal design.

Résumé en français

Cette thèse en psychologie Clinique propose de rallier le concept de schizotypie avec la dimension du Soi en utilisant une approche trait-état. La dimension du Soi est au cœur du continuum de la psychose selon le courant phénoménologique et pourtant absente des définitions contemporaines de la schizotypie. Ce projet s'attèle à l'étude de la schizotypie en lien avec les anomalies de l'expérience de soi (ASE) et leurs sous-bassement neurobiologiques respectifs dans la population générale. La schizotypie, représente un trait de personnalité, distribué normalement dans la population générale, qui dans son expression extrême, peut être considéré comme un facteur de risque du développement de la psychose. Les ASEs s'expriment quant à elles, à la manière de phénomènes subtiles, observables à l'état non psychotique chez l'individu sain, mais également au cours du prodrome de la schizophrénie. Un grand nombre d'études ont montré que les anomalies relatives au soi sont plus fréquentes chez des individus qui développent des troubles du spectre de la psychose et dans le cadre de cette thèse, elles seront provoquées expérimentalement de façon à reproduire un état s'apparentant aux symptômes observés dans les états à haut risques. Dans ce contexte nous nous penchons sur le développement de ces deux facteurs de risques, ainsi que de leur potentielle interaction dans le but d'améliorer la compréhension des premières étapes du risque psychotique. Cette thèse s'inscrit naturellement dans le récent intérêt de la recherche dirigé vers la détection précoce. La démarche longitudinale et le caractère multimodal des analyses conduites apportent une force supplémentaire à ce travail de thèse dont le but final est d'étudier les liens entre schizotypie, ASEs, et certains facteurs développementaux, comportementaux et cérébraux, au sein d'une population au développement typique. Dans l'ensemble du projet, une tâche spécifique est utilisée pour induire des ASEs de manière expérimentale ; la tâche du miroir.

Les deux premières études permettent d'identifier les trajectoires développementales de l'épaisseur corticale et des volumes des noyaux sous corticaux en fonction des différentes dimensions de la schizotypie pendant l'adolescence. La troisième étude, comportementale, a pour but de mieux caractériser et définir les ASEs et leurs spécificités en fonction de l'âge dans le contexte de la tâche du miroir. Dans la quatrième étude, nous mettons en place une étude en IRM fonctionnelle qui permet d'étudier les corrélats neuronaux précédant, pendant et suivant l'apparition d'une illusion induite par la tâche du miroir. Finalement, nous mettons en valeur la relation entre les anomalies du soi et les réseaux neuronaux au repos, de manière transversale et longitudinale.

List of abbreviations

ACC: Anterior Cingulate Cortex

AD: Average Distance

ADHD: Attention-Deficit/Hyperactivity Disorder

ADM: Average Distance Between Means

ASE: Anomalous self-experiences

APM: Average proportion of non-overlap

APS: Attenuated positive psychotic symptoms

BBL: Brain Behavioral Laboratory

BIC: Bayesian Information Criterion

BOLD: Blood Oxygenation level-dependent

BLIPS: Brief limited intermittent psychotic symptoms

BS: Basic Symptoms approach

BSABS: Bonn Scale for the Assessment of Basic Symptoms

CAADS: Clinician Administered Dissociative States Scale

CAARMS: Comprehensive Assessment of At-risk mental states

CHR: Clinical high risk

CMS: Cortical Midline Structures

COGDIS: Cognitive disturbances

COPER: Cognitive-perceptive basic symptoms

CT: Cortical thickness

dACC: dorsal Anterior Cingulate Cortex

dMPFC: Dorsomedial prefrontal cortex

DMN: Default mode network

DPD: Depersonalization disorder

DSM: Diagnostic statistical manual

EASE: Examination of Anomalous Self-Experiences

ESM: Experience Sampling Method

FEP: First episode psychosis

FOM: Figure of Merit

FSIQ: Full Scale Intelligent Quotient

GM: Grey Matter

Hg: Hemoglobin

HDS: High disorganized scorers

HNS: High negative scorers

HPS: High positive scorers

HS: High schizotypy

ICD-10: International Classification of Diseases

IS: Intermediate schizotypy

IDM: Ipseity-disturbance model

IQ: Intelligence Quotient

LDS: Low disorganized scorers

LNS: Low negative scorers

LPS: Low positive scorers

LS: Low schizotypy

MGT: Mirror Gazing Task

mOFC: Medial orbital prefrontal cortex

mPC: Medial prefrontal cortex

MRI: Magnetic resonance imaging

pACC: Pregenual anterior cingulate cortex,

PAM: Partition around medoids

PCA: Principal Component Analysis

PCC: Posterior cingulate cortex

PET: Positron emission tomography

PF: Prefrontal

PFC: Prefrontal cortex

PLE: Psychotic like experiences

Rs-fMRI: Resting State-fMRI

RHS: Revised Hallucination Scale

RSC: Retrospenial cortex.

SACC: Supragenual Anterior Cingulate Cortex

SD: Schizotypal disorder

SIPS: Structured Interview for Prodromal Symptoms

SPQ: Schizotypal Personality Questionnaire

SPD: Schizotypal Personality Disorders

TD: Typically developing

UHR: Ultra-high risk

vmPFC: Ventromedial prefrontal cortex

WAIS-IV: Wechsler Adult Intelligence Scale

WISC-IV: Weschler Scales of Intelligence for children

WM: White matter

Table of Contents

Chapter I

Theoretical background

Psychotic disorders, referred to as Schizophrenia spectrum and other psychotic disorders (American Psychiatric Association, 2013), are conceptualized as neurodevelopmental disorders, and represent the most costly brain vulnerabilities in Europe, accounting for 93.9 billion of the total cost of brain disorders of 798 billion Euros in 2010 (Olesen et al., 2012). The full-blown clinical picture typically emerges during late adolescence and early adulthood. To further understand the mechanisms underlying these disorders, consideration must be given to risk factors both proximal and distal to onset of the disorder. The study of subclinical manifestations of schizotypy and anomalous self-experiences (ASEs) as potentially reflecting cognitive or biological vulnerability to psychosis in the general population, gives us the opportunity to research relevant distal risk markers. Although these vulnerabilities remain dormant and unexpressed unless triggered by adverse environmental exposure, understanding their typical developmental course can provide new insights about trajectories that may lead to higher risk states.

1. Introduction overview: TRAIT – STATE approach

> "It is one thing to be irascible, quite another thing to be angry, just as an *anxious temper* is different from *feeling anxiety.* Not all men who are sometimes anxious are of an anxious temperament, nor are those who have an anxious temperament always feeling anxious" Cicero (45 B.C).

The distinction proposed by Cicero has been widely used in psychology, with the aim of characterizing and identifying behavioral and biological markers that are intrinsic to various disorders and has been used in the field of schizophrenia to aim at the identification of targets for early detection and prevention. A trait marker is characterized by behavioral and biological properties playing a potential causal role in the emergence or predisposition of psychopathologies, making the trait enduring or latent. Whereas a state marker corresponds to a transient marker, it reflects the phenomenological manifestation of the risk to develop psychosis (Chen et al., 2006). This trait versus state duality is highlighted as controversial in psychiatry and psychology (Stoyanov & Kandilarova, 2014), raising the question: which of trait personality or state phenomenon accounts for the apparent variability in human behaviors. However, Claridge and Davis (Claridge & Davis, 2003) pointed out the two accounts of mental disorders necessary to understand abnormal behaviors: the "trait-like personality" and the "symptom-state illness". Thus, in the present work we propose that this duality can be fertile for early psychosis research, as we hypothesize that the personality trait might provide a basis for the proneness to expression of transitory sub-clinical states. Thus, we follow Claridge and Davis's view considering that the state might derive from the personality trait.

First, we study schizotypy as a personality trait marker incorporated in the continuum model of schizophrenia. Therefore, schizotypy can be defined both as enduring psychological features varying along the continuum, as well as a varying predisposition to psychotic disorders. Second, we will investigate the state of anomalous self-experiences through an experimental approach, as in subtle disturbances of the self - triggered by the mirror gazing task. This second element represents a unique candidate for monitoring and understanding visual perceptual changes that exist in psychosis before the clinical onset.

This introductory chapter will be divided in two sections. The first will review the concept of schizotypy, explaining its relevance in the field of psychotic disorders, notably in the detection of early psychosis through its links with analogous samples. Moreover, an overview of structural neural correlates of schizotypy dimensions will emphasize the lack of longitudinal studies investigating the course of schizotypy and brain maturation during the critical period of adolescence. In the present thesis, the term psychosis or psychotic disorders will be preferred to schizophrenia, referring to the presence of psychotic symptoms as phenomena characterizing the disorder of schizophrenia and attenuated versions associated with its extended phenotype.

Secondly, we posit that another way to look at psychotic disorders is to experimentally induce a transient state that resemble clinical symptoms observed along the spectrum, notably high-risk state symptoms. Adolescence represents not only a major period of interest for brain maturation but also for development of the self-identity, and because the phenomenologists believe schizophrenia is a disorder of the core self, we propose an in-depth examination of experimentally induced anomalous self-experiences (ASEs). We will consider ASEs as a manifestation of a state-like symptom deriving from schizotypal traits, such as perceptual disturbances while including a dimension of the self.

Firstly, clinical observations of alterations of perception of the self will be presented, notably the mirror phenomenon observable along the spectrum of psychotic disorders. We will present briefly the theoretical account of phenomenology placing disturbances of the self as the core mechanism of schizophrenia disorders, and the presence of anomalous self-experiences along the spectrum. Literature on depersonalization will be briefly reviewed as a potential manifestation of the mirror phenomena. Following this, we will detail the use of sensory deprivation to induce a state manifestation resembling that of the mirror phenomenon. And subsequently will we detail the use of the mirror-gazing task to induce such sensory deprivation and trigger ASEs and depersonalization phenomena. Furthermore, contribution of the field of Bayesian perception processing will provide a potential background to understand the mechanisms of apparitions of such unusual perceptions and will be linked to neural correlates of dynamic representations of the self as well as those of pathological hallucinations.

The final section will outline the rationale of the project, hypotheses that were investigated and the studies that were conducted to answer our general research question.

2. The concept of schizotypy

2.1 Historical account and background

The concept of schizotypy was introduced in a developmental perspective by Emil Kraepelin (1919) and Eugene Bleuler (1911), (Moskowitz & Heim, 2011) who both described subclinical expressions or schizophrenic-like traits in patients before the onset of psychosis. However, the term "schizotype" was first used by Sandor Rado (1953) as a shortened derivative of "schizophrenic phenotype", and characterized individuals presenting impaired body awareness and experience of pleasure (Rado, 1953). Other symptoms were thought to stem from these central features, as attenuated similar traits were observed in relatives of patients (Kendler, 1985). Paul E. Meehl then introduced the notion of "Taxons", considering that a specific gene is the cause of abnormal development of the central nervous system leading to "schizotaxia", characterized as thought disorders, anhedonia, interpersonal problems and ambivalence. Meehl's quasi-dimensional approach assumed other factors such as the environment or other genes that could interact with the small percentage of the individuals carrying this schizotype and would eventually lead to diagnosable psychosis, whereas the majority would remain "compensated schizotypes".

An alternative account of the schizotypy concept can be found in the "fully dimensional" model, which proposes a continuum from healthy functioning individuals to those with a clinical diagnosis (Claridge & Beech, 1995; Van Os & Jones, 2001). This model has roots in the work of Eysenck who emphasized *individual differences* in personality and posits that psychoticism represents the extreme end of a continuum (Eysenck, 1976). Schizotypy is

therefore considered a dimension of personality normally distributed throughout the general population; thus, representing a healthy trait that sustain schizotypal expression which when exacerbated augment the risk for significant psychotic outbreak. Schizotypy is regarded as a measure of psychosis proneness, as a liability trait marker for the development of schizophrenia (Lenzenweger, 2010).

2.2 Schizotypy as a model of schizophrenia

Considering schizotypy as a model of schizophrenia has benefits for research. Because individuals who score high on schizotypy measures do not typically present effects of chronic illness (i.e. medical treatment and/or hospitalizations), we may be able to investigate underlying risk factors for psychotic symptoms without the confounds that come with the illness itself (Cadenhead & Braff, 2002). The construct of schizotypy encapsulates the phenotypic expression of vulnerability to schizophrenia, involving subtle but clinically relevant abnormalities in interpersonal functioning, thoughts, perception and/or emotions. It is also considered as a part of typical personality, which may nevertheless constitute a ground for the development of psychosis (Claridge & Beech, 1995).

The general consensus is that schizotypy follows an heterogenous multidimensional structure that underscore key features used in the latest Diagnostic Statistical Manual (DSM) versions to identify the key features of the schizophrenia spectrum, with positive (cognitive-perceptual), negative (interpersonal), and disorganized dimensions (Raine et al., 1994; Fonseca-Pedrero et al., 2009; Nelson et al., 2013; Barrantes-Vidal et al., 2015; Cicero, 2016; Davidson et al., 2016). The positive dimension reflects the tendency to undergo unusual cognitive and perceptual experiences – including oddities in all senses and ranging from illusions to hallucinations, it is characterized by disruptions of thoughts content – including magical ideation, superstitious beliefs and delusions, and suspiciousness and paranoia. The negative dimension involves

inability or diminution to experience pleasure from social and physical stimuli and includes: flattened affect, lack of close friends and social withdrawal conferring a disinterest in others and the world. And the disorganized dimension denotes a tendency toward disorganization of thoughts and behaviors, ranging from mild disturbances in thinking and behaviors to thought disorder and disorganized actions (Reynolds et al., 2000). In Table 1, examples are given for each of the nine subscales features.

SPQ Subscales	Examples from SPQ items
Ideas of reference	Feeling that what is seen on TV or read in the newspaper has a special meaning When going out, sensation of being noticed
Excessive social anxiety that goes not diminish with familiarity	Avoid going to places where there will be many people because of anxiety Nervous during polite conversations Nervous when someone walks behind
Odd beliefs or magical thinking (superstitiousness, belief in clairvoyance, telepathy, "sixth sense", bizarre preoccupations)	Experiences with the supernatural Beliefs in telepathy, mind reading, clairvoyance
Unusual perceptual experiences, including body illusions	Mistake objects and shadows for people, noises or voices When looking in the mirror, changes in the face Hearing a voice speaking inner thoughts aloud
Appearance and behaviors odd, eccentric or peculiar	Seen as eccentric or odd Seen as as a little strange by others
Lack of close friends and/or confidants other than first-degree relatives	Little interest in getting to know other people Quiet when with other people Difficulties to be emotionally close to other people
Odd speech and thinking (i.e. metaphorical, stereotyped, vague, circumstantial, overelaborate)	Others find it hard to understand the speech Jump from one topic to another when speaking Ramble on too much when speaking
Inappropriate or constricted affect	Seen as aloof or distant Rarely laugh and smile Poor at returning social courtesies and gestures
Paranoia ideation and suspiciousness	Think people are talking behind their back Concerned that friends or coworkers are not loyal or trustworthy

Table 1: Examples for each of the nine subscales taken from the items of the self-reported Schizotypal Personality Questionnaire (SPQ)

Although a consensus exists agreeing that schizotypy construct is a multifaceted concept, there remains a lack of agreement on its core dimension and the relative influence of each. The question arises whether individuals with negative schizotypal features would be more likely to develop more severe psychological illness, or whether individuals with positive schizotypal

features would be at higher risk for potential development of schizophrenia spectrum disorders, and what is the role of the disorganized features in the triad. In general, there is more evidence for the continuous distribution of positive schizotypy (Edens et al., 2009) than for negative schizotypy (Ritsner, 2014). The majority of developmental studies have targeted transient positive manifestations and successfully identified them as predictors of increased risk for psychotic disorders (Cougnard et al., 2007; Poulton et al., 2000). However, recent findings proposed that polygenic risk scores for schizophrenia are inversely correlated with the positive dimension of schizotypy in the general population (Hatzimanolis et al., 2018; Zammit et al., 2014), suggesting that schizophrenia-related genetic contribution did not predict the transition to schizophrenia spectrum disorders but could hypothetically predict psychosis spectrum disorders instead. On the other hand, the negative dimension was associated with conversion to psychosis in clinical high risk patients (Flückiger et al., 2016). Confirming these findings, a meta-analysis conducted on 7282 individuals from the general population suggested that the positive dimension predicts later emergence of psychotic disorders, whereas the negative dimension is selectively associated with emergence of non-psychotic schizophrenia-spectrum disorders (Debbané et al., 2015) . Although none of the studies included in this meta-analysis included the disorganized dimension, another study investigated the potential contribution of disorganized features in the general population (Debbané et al., 2013). They were found to mediate the progression of positive schizotypy, notably during early adolescence, suggesting that the interaction between positive and disorganization features might heighten the risk of psychosis during adolescence.

Measurements of schizotypal features encompass a wide range of self-report and interview-based instruments. The most widely used questionnaires include those measuring specific dimensions of schizotypy, such as positive (i.e. Perceptual Anhedonia Scale) or negative

symptoms (Physical and Social Anhedonia Scales), and those capturing the multidimensional features of schizotypy (i.e. Schizotypal Personality Questionnaire, SPQ). The SPQ is the main measure of schizotypal features in this PhD thesis, it was developed based on the DMS-III-R clinical definition of schizotypal personality disorders (SPD), (American Psychiatric Association, 1987)). SPD prevalence rates reach a percentage of 2-3%, which is higher than the prevalence of schizophrenia (Cadenhead & Braff, 2002). SPD and schizophrenia are thought to share similar etiological and pathophysiological mechanisms, and also similar cognitive deficits (Trestman et al., 1995). Consensus on SPD posits that it represents a trait marker for the development of psychosis spectrum disorders and is used as a criterion to detect individuals in the prodromal stages of schizophrenia (Yung et al., 1996a), and scores on the SPD dimensions were found to predict individuals that would convert to psychosis (Mason et al., 1995). In the previously mentioned meta-analysis of longitudinal studies, involving 376 patients followed for 2 to 20 years, the rate of conversion from SPD to schizophrenia-spectrum disorders was of 11.4%, which was almost equivalent to the 11.9% of conversion rate observed in schizophrenia patients' relatives (Debbané et al., 2015).

These findings highlight the evidence of predisposition to psychosis that can manifest as schizotypal features, justifying that schizotypal personality shares at least some genes with schizophrenia and can be considered an endophenotype for psychosis spectrum disorders (Lenzenweger, 2006), in the sense of measurable traits on the pathway to the disease sharing some of the biological mechanism observable in clinical states. Therefore, the use of SPQ as a measure of stable psychosis-like trait manifestations is justified, since it takes part in the predisposition to psychotic disorders.

2.3 Early emergence of psychosis and conversion rates

In understanding psychosis, interest has grown in the use of analogue samples, including individuals at *genetic risk,* such as patients' relatives: *clinical high risk*, defined by help-seeking individuals with subclinical psychotic experiences; and people in the general population with heightened expression of "schizotypal" features. These analogue samples share similar biological and psychological traits as well as etiological factors (van Os et al., 2009; Cadenhead & Braff, 2002).

The identification of genetic risk encompasses family history of psychosis or individuals with schizotypal personality disorders presenting a decline in functioning or sustained low functioning.

Two contemporary views are considered when identifying individuals in a clinical high risk (CHR) state. On one hand, the **ultra-high risk** (UHR) (Yung et al., 1996) phenomenology significantly overlaps with that of schizotypal traits but differs on the fact that UHR states reflect an impact on individual's functioning, whereas schizotypal traits consist in manifestations that individuals recognize as stable manifestations. UHR criteria identifies three groups of clinical high-risk patients: *attenuated positive psychotic symptoms* (APS); *genetic risk,* such as familial risk or schizotypal personality disorder; and *brief limited intermittent psychotic symptoms* (BLIPS), which lie bellow DSM criteria for brief psychotic episode's duration. APS represent subthreshold attenuated positive symptoms. To identify them on the structured interview for psychosis-risk syndromes (SIPS) (McGlashan et al., 2010), one or more items should reach a score of 3 to 5 on unusual thought content and delusional ideas, grandiose ideas, suspiciousness and persecutory ideas, perceptual abnormalities and hallucinations and disorganized communication, with a frequency of at least once a week in the past month and a first onset within the past year. APS have also been described in the DSM-V, in which one or more of the following criteria are necessary to identify them:

attenuated forms of delusions, hallucinations and disorganized speech, with a first appearance within the past year and a frequency of at least once a week. BLIPS identify fleeting psychotic experiences that spontaneously resolve, they are defined as transient psychotic symptoms in the subscales of unusual thoughts content, "non-bizarre" ideas, perceptual abnormalities, disorganized speech with a duration inferior to 1 week and an emergence within the past 12 months according to the Comprehensive Assessment of At-risk mental states (CAARMS (Raballo, Nelson, et al., 2011)). On the SIPS they are identified as transient psychotic symptoms in the realm of hallucinations, delusions, disorganization, with an intermittence of several minutes per day, occurring at least once a month and with an onset within the past 3 months. Diagnosis of SPD is based on the Schizotypal personality Questionnaire (DSM-IV) and requires 5 or more symptoms of odd beliefs or magical thinking, suspiciousness or paranoid ideation, odd thinking and speech and/or constricted affect and social anxiety, with stable symptoms leading to clinical distress and impairment in social and occupational life and functioning and an enduring long duration with an onset identifiable in adolescence and early adulthood.

On the other hand, **the Basic Symptoms approach** (BS) focuses on the detection of the earliest possible specific symptoms, in terms of subtle subclinical self-experienced disturbances (Schultze-Lutter, 2009). The basic symptom criteria include cognitive-perceptive basic symptoms (COPER) and cognitive disturbances (COGDIS). COPER basic symptoms include thought interference and blockage, disturbances of receptive speech, ideas of reference, thoughts perseveration, inability to discriminate between fantasy and true memories, and visual and acoustic perception disturbances. They require 1 of the 10 basic symptoms, with a weekly occurrence and a first occurrence at least in the past 12 months. COGDIS disturbances encompass subtle disturbances of self-experiences of perceptual processes in the visual,

acoustic, thoughts and speech domains and require 2 of 9 cognitive basic symptoms with an occurrence of once a week and an onset in the past 3 months (Schultze-Lutter et al., 2016). Schizotypal disorder (SD) have been defined with the use of the International Classification of Diseases (ICD-10) (World Health Organization, 2019), and require at least 4 of the criteria within odd beliefs or magical thinking influencing behavior, suspiciousness or paranoid ideas, unusual perceptual experiences including body illusions or depersonalization, derealization, odd speech and thinking (including vague, circumstantial, metaphorical, overelaborated thinking and speech), with a continuous or repeated frequency, and symptoms manifested over at least 2 years.

The conversion rate of CHR (UHR or BS) was estimated at 18% at six months, 22% after a year, 29% at two years, and 36% at three years (Fusar-Poli et al., 2013). A recent review investigated the conversion rates to psychosis in four different samples (Debbané et al., 2015). In the first sample of 369 clinical high-risk patients, 172 converted to psychosis (46,6%). The genetic high-risk sample encompassed 637 offspring of patients diagnosed with schizophrenia, from which 76 converted to general psychosis (including schizophrenia, 11,9%). Thirdly, from a group of 376 patients diagnosed with either SPD, self-disorders, or schizoid personality disorders, 43 developed psychosis spectrum disorders (11,4%). Concerning schizotypy, the prevalence is harder to predict. Mainly because there are no cut-off scores and because schizotypy might not always be fully expressed. However, when combining six longitudinal studies including 7282 participants from the general population, 207 of them converted to psychosis (2.8%, Debbane et al., 2015). Beyond a three to five years interval, assessment of schizotypy represent an equally, if not better, predictor of psychosis, conferring a distal predictive value of the risk for psychosis (Debbané et al., 2015; Debbané & Barrantes-Vidal, 2015a). The six aforementioned studies (Bogren et al., 2010; Chapman et al., 1994; Gooding

et al., 2005; Kwapil, 1998; Kwapil et al., 2013; Miettunen et al., 2011) suggested that the negative dimension of schizotypy (especially anhedonia) was associated with the development of schizophrenic-spectrum disorders without psychosis, while the positive dimension was linked to the emergence of psychotic disorders. Of note, little is known about the role of the disorganized dimension that has been hardly studied. Therefore, it is worth keeping in mind that some effects might be misattributed to the positive or negative dimensions.

2.4 "Happy" schizotypes

The personality-based framework also allows for the existence of benign aspects of schizotypy which become pathological only when expressed in excess. This is particularly true for higher expressions of the positive dimension. For example, individuals expressing personal enlightenment, interconnectedness with others, or spirituality have not transitioned to pathogenesis, and, in these cases, positive schizotypy might represent a potential protective factor (Mohr & Claridge, 2015). In their review, Mohr and colleagues proposed that higher expression of positive schizotypy was associated with personal wellbeing, favorable personality traits and psychological features (i.e. openness to experience and fantasy proneness), and unconventional thinking (notably creativity).

2.5 Developmental evolution of schizotypy levels

The ontogeny of schizotypy in the general population has been investigated but is still not clear. Geng and colleagues (Geng et al., 2013) followed college students for 18 months and identified three types of trajectories: a low schizotypy group that kept decreasing over time, a high schizotypy group that kept increasing and a medium group that remained stable over time. In another study, Wang and colleagues (Wang et al., 2018), demonstrated that the "stable high schizotypy group" displayed the worst clinical and functional outcomes and the "high reactive

schizotypy" group was characterized by a rapid decline in functioning. When comparing individuals according to age, younger participants tend to score higher on the scales and dimensions of schizotypy than older ones. This pattern was found between college and university students (Fossati et al., 2003a), as well as in adults populations (Badcock & Dragović, 2006a). With age, adolescents' scores on schizotypal subscales increased, especially those between 12 and 15 years old (Fonseca-Pedrero et al., 2008). The increase of schizotypy levels suggest that adolescence is a period of heightened expression, preceded by lower features in childhood and subsequent decline along adulthood. Importantly, certain features of schizotypal personality expressed during maturational processes may develop earlier than others (DiDuca & Joseph, 1999) and/or vary with age (Chen et al., 1997). Furthermore, most studies investigating the evolution of schizotypy levels are based on cross-sectional findings, thus there is a lack of longitudinal studies following the transition period from childhood to adulthood through adolescence.

2.6 Schizotypy and adolescence

The reduction of schizotypy level seems to coincide with the transition from adolescence to adulthood sustained by developmental maturational processes (Debbané et al., 2013). Along this period, behavioral, physiological and neurodevelopmental changes are happening, making this transitional stage crucial for the typical reduction in schizotypal levels. Typical psychological development occurs during adolescence, with a striving for individuality, maturation of identity, appreciation of the outside world, perceived usefulness of conventions and beliefs, and a decline of impulsivity and attention seeking (Cohen et al., 2005). Late adolescence also represents the period for the onset of psychopathologies, making it a key developmental period for the emergence of schizophrenia spectrum symptoms (Häfner et al.,

1994; Paus et al., 2008). Furthermore, this period is also accompanied by important brain structure maturational changes that will be discussed below.

2.7 The adolescent's structural brain

Brain imaging techniques have widened the opportunities to study the brain's basis of psychological phenomena and offer important additional information. Psychotic disorders being considered as neurodevelopmental and during adolescence – especially brain maturational trajectories during this period – might reveal crucial insights into the mechanisms underlying this spectrum of disorders. Several studies have investigated the developmental trajectories of grey matter maturation, which is considered as the most strongly age-related parameter when it comes to brain measures (Tamnes et al., 2010). Hence, in the present thesis we focus on two gray matter measures: cortical thickness and subcortical volumes.

The main observation coming from studies using mixed model regression analyses is a decrease of **cortical thickness (CT)** in most of brain regions, starting as early as the age of 5 (Ducharme et al., 2016; Vijayakumar et al., 2016; L. M. Wierenga et al., 2014). However, when analyzing CT in key age windows for cognitive processes, different results emerged. Significant thickening of the cortex was observed in frontal and perisylvian regions in children aged between 5 and 11 years old (Sowell et al., 2004), two regions involved in development and understanding of speech. The same study showed that the left hemisphere's cortical thickness greater thinning was associated with vocabulary improvement. Another study focusing on social brain regions (social cognition and mentalizing mechanisms) found that cortical thickness decreased linearly from childhood to early adulthood, except in the anterior temporal cortex which plays a role in socio-emotional processing (Olson et al., 2007), where it increased with quadratic trajectory until early twenties (Mills et al., 2014). Confirming this last finding,

limbic system regions presented differential development during adolescence (Casey et al., 2008). A consensus was reached by many studies, showing an early maturation of cortical thickness of primary sensorimotor regions followed by a later development of higher order association and paralimbic regions (Gogtay et al., 2004; Khundrakpam et al., 2013).

When looking into **cortical grey matter volume**, the maturation is characterized by inverted U-shaped developmental trajectories in most brain regions. Frontal grey matter volume displayed a peak around age 11 in females and age 12.1 in males, while temporal regions volumes peaked around age 16.5 (Giedd, 2004). Another study from 2015 also showed that grey matter volume in most brain regions decreased after reaching a peak at around 8 years old (Bray et al., 2015).

Regarding **subcortical grey matter volume**, longitudinal studies of early life have shown volumes increases in the hippocampus and caudate nucleus (Holland et al., 2014). Following childhood, the trajectories of individual structures started to diverge, with the thalamus following a quadratic volume trajectory until age 18, and a linear decrease starting at age 20 (Walhovd et al., 2011), while the basal ganglia followed general linear decreases until 18 years of age (Brain Development Cooperative Group, 2012). A longitudinal study showed that the globus pallidum, striatum and thalamus underwent increases and subsequent decreases of volume during development with respective peak ages of 8-10, 12-15 and 14-17 (Raznahan et al., 2014). Moreover, hippocampus and amygdala showed inverted U-shape trajectories from childhood to puberty (Ostby et al., 2009). The quadratic developmental trajectory pattern of grey matter volume observed in adolescents' brain was confirmed by Narvacan and colleagues (Narvacan Karl et al., 2017), who investigated deep grey matter subcortical structures, such as thalamus, caudate, putamen, pallidum, nucleus accumbens, hippocampus, and amygdala.

However, in their study, they located the peak of grey matter volume around the age of 10-13 for most subcortical structures.

To sum up, adolescence therefore represents a key period for healthy maturational processes, as it is accompanied with increased vulnerability, adjustments and emotional reactivity. Prefrontal cortices, sustaining cognitive control and emotional regulation, are some of the last regions to reach maturation; in contrary to primary brain regions associated with motor and sensory functions that are already mature at a younger age. Loss of grey matter appears first in primary sensorimotor areas, followed by dorsolateral prefrontal and lateral temporal cortices during adolescence. Higher order association cortices develop after lower-order cortices, such as primary visual and primary somatosensory cortices (Gogtay et al., 2004). Overall, the limbic system develops before prefrontal control regions, which is believed to create a bias towards suboptimal decisions and actions in adolescents when compared to children, where both systems are still developing, and to adults who display fully developed systems (Casey et al., 2008).

On the basis of this literature, we wish to investigate the developmental trajectories of cortical and subcortical structures in typically developing adolescents and young adults expressing heightened schizotypal traits. Thus, it is of importance to bear in mind the typical trajectories of cortical and subcortical brain maturation, in order to identify the similarities and differences associated with schizotypy and along the spectrum of psychotic disorders.

The following sections will first detail alterations observed along the schizophrenia continuum, and secondly, we will review the potential candidate structural brain regions associated with the expression of positive, negative and disorganized schizotypy traits.

2.8 Structural neural correlates along the schizophrenia continuum

At the clinical endpoint of the continuum, neuroimaging studies reported brain structures alterations in schizophrenia-diagnosed individuals, including grey matter volume reductions across the cortex, hippocampus and amygdala (Cannon et al., 2015; Chua & McKenna, 1995). In addition, subcortical volumes alterations frequently replicated in schizophrenia included; smaller bilateral hippocampi, amygdala, thalamus, nucleus accumbens and intracranial volumes, as well as larger lateral ventricle and pallidum volumes (Haijma et al., 2013; Olabi et al., 2011). First episode psychosis patients (FEP) showed CT alterations localized in frontal (Asmal et al., 2018) and temporal areas (Dickey et al., 2002; Janssen et al., 2009), as well as volumetric reductions in hippocampus (Adriano et al., 2012), right caudate (Ellison-Wright et al., 2008), and thalamus (Gilbert et al., 2001).

Studies investigating stages prior to the onset of the disorder have accumulated evidence in at-risk subjects who go on to develop psychotic disorders, which suggest atypical brain morphology (Ziermans et al., 2012) and atypical patterns of cerebral maturation (Schneider et al., 2014). Following clinical high-risk individuals, a steeper rate of thinning was observed in medial and lateral prefrontal regions for converters in comparison to non-converters (Cannon et al., 2015). Young CHR converters also exhibited smaller surface area in rostral anterior cingulate, prefrontal regions and para hippocampal gyrus (Chung et al., 2019). Additionally, CHR who converted to psychosis exhibited less gray matter volume in the left para hippocampal cortex than those who did not convert (Mechelli et al., 2011). In terms of subcortical structures, reductions in hippocampal (Fusar-Poli et al., 2012) and thalamic volumes (Harrisberger et al., 2016) have also been described. When considering patients with SPD, a review identified structural brain alterations in superior temporal gyrus, para hippocampus and thalamus (Dickey et al., 2002; Ettinger et al., 2014; Janssen et al., 2009), as

well as hippocampus and lateral ventricle (Buchsbaum et al., 1997; Cannon, 1994; Dickey et al., 2002; Fervaha & Remington, 2013).

Taken together, these results imply that cortical and subcortical thickness and volume alterations are already observable at the earliest stages of the clinical manifestations of schizophrenia spectrum and other psychotic disorders. Nevertheless, factors such as severity of symptoms, psychological impact of hospitalization, and antipsychotic treatment potentially contribute to the morphological modifications of the brain observed along the development of spectrum disorders (Jørgensen et al., 2016; Moncrieff & Leo, 2010; Navari & Dazzan, 2009). Thus, studying schizotypy offers a unique framework to observe neurobiological mechanisms involved in psychosis phenotypes, while avoiding confounding effects of collateral factors, such as medication and disease progression.

2.9 Structural neural correlates of schizotypy

Studies on brain morphology in the general population in relation to self-reported scores on schizotypy measures have identified disparate results (DeRosse et al., 2015; Ettinger et al., 2014; Evans et al., 2016; Modinos et al., 2018; Moorhead et al., 2009; Nenadic et al., 2015; Wiebels et al., 2016; Zou et al., 2015). Studies reported that adults scoring higher on the SPQ total score (DeRosse et al., 2015) and individual dimensions (Wiebels et al., 2016) typically showed less gray matter volume and cortical thickness in the frontal and temporal lobes, as well as anterior cingulum and insula (Moorhead et al., 2009; Zou et al., 2015). In contrast, two studies reported that higher scorers on positive dimension presented with greater grey matter volumes in posterior cingulate cortex and precuneus (Modinos et al., 2018; Nenadic et al., 2015). Only two cross-sectional studies examined schizotypy during adolescence. The first study showed that youths (16-23 years old) with high schizotypy displayed lower grey matter density in the insula and dorsolateral prefrontal gyrus (Wang et al., 2015). The second study,

found that youths (6-17 years old) with higher level of positive schizotypy showed decreased grey matter density in temporal and caudate volumes (Evans et al., 2016). In addition, adolescents experiencing subclinical psychotic experiences showed volumetric enlargements in the left hippocampus, right caudate and right lateral ventricle (Naohiro Okada et al., 2018). Kuhn and colleagues (Kühn et al., 2012) showed a correlation between high schizotypy total scores and reductions in thalamic volume.

These studies suggest that detailed examination of the associations between the expression of schizotypal personality features during adolescence and morphological brain development may reveal relevant information to understand schizophrenia spectrum and other psychotic disorders. To date, studies investigating psychometric schizotypy have employed cross-sectional designs with success in identifying cerebral alterations linked to the expression of schizotypy, but their ability to provide information about developmental trajectories is limited. Hence, to fill the gap existing in the reviewed literature, using longitudinal studies offers the opportunity to better understand the developmental brain maturation of schizotypal features in adolescence and early adulthood. Furthermore, previous findings have been shown to be disparate, calling for the need of novel studies integrating diverse brain measures and including larger samples of individuals expressing schizotypy traits.

To summarize this second section, the concept of schizotypy and its historical origins were detailed, and a review of its account in the continuum of psychotic disorders was provided. We underlined that schizotypy is a more than suitable candidate basis to contribute to and inform preventive research in psychotic disorders, notably in its capacity to detect typically developing individuals who are the most vulnerable to psychosis. We reviewed the literature concerning the development of structural cortical and subcortical regions of the brain that presented abnormalities along the psychosis spectrum and those that could constitute at-risk targets when associated with heightened levels of schizotypy. However, we noted that there remains a lack of longitudinal studies in the existing literature along the critical period from adolescence to young adulthood, and little is known about the neural underpinnings of individual dimensions of schizotypy.

In light of the longitudinal evidence supporting the link between schizotypy and psychotic disorders, individuals with heightened expression of schizotypy represent a valuable population in which to study sub-clinical forms of psychotic symptomatology. Thus, taking roots in the early detection of psychosis current, another way of looking at psychotic disorders is to focus on 'high risk state symptoms' that we could experimentally trigger in individuals from the general population expressing schizotypal personality traits.

In the following section, we propose a 'state' approach that derives from the inclusion of schizotypy as trait-like enduring risk marker for psychosis. Inducing short-term sensory deprivation results in transient states phenomena resembling the symptoms seen in clinical high-risk populations. Thus, in the next section we introduce an experimental procedure that induces attenuated forms of anomalous-self experiences, ranging from appearance of light and colors to depersonalization-like phenomena.

3. The concept of anomalous self-experiences

Under this section, we wish to draw attention to clinical manifestations of self-disturbances that may be observable in the prodromal and even premorbid stages of schizophrenia spectrum disorders. More specifically, the present thesis focus on the mirror phenomenon, observable in patients with schizophrenia who reported strange face illusions when staring at their own faces in the mirror. We conceptualize such experiences as anomalous self-experiences. In line with the importance of early diagnostic detection and therapeutic interventions, anomalous self-experiences might be recognized as a potential phenomenological state that could inform on the occurrence of clinical hallucinations. Firstly, we will present clinical observations of alterations of self-perception, more specifically the mirror phenomenon. We will review the influence of phenomenological theories that place subjective self-disturbances within the continuum of psychotic disorders. Then, we will develop the account of depersonalization state and its link with ASEs and the mirror phenomenon. Following this, we will propose a novel approach to study subjective experiences in psychopathology, using sensory deprivation to induce ASE-like states, as in perceptual illusions of the self, and propose the mirror gazing task to induce such states in typically developing individuals. Subsequently, contribution of predictive coding modelling of subjective perceptual anomalies and its roots in Bayesian theories of perception will be detailed. Ultimately, we will review existing literature identifying neural correlates related to self-perception and emergence of visual hallucinations.

3.1 The Mirror phenomenon: clinical descriptions

The mirror phenomenon was defined by Harrington (Harrington et al., 1989) as a strong perceptual disturbance that one's own face reflection in the mirror is changed, distorted, or "taking on a life of its own". The perceptual illusion continuously changed, and the expressions observed in the mirror were most of the time threatening, and eyes and mouth seemed to be the most affected facial features. It has been observed that schizophrenia patients confronted with their own image in the mirror reported impressions that their reflection was distorted, independently of themselves, and psychiatrists attested of schizophrenic patients draping mirrors in their home to avoid catching a glimpse of their own reflection (Harrington et al., 1989).

In addition, in high-risk states patients, two scales have been designed to detect subjective anomalous experiences in the prodrome of schizophrenia, including the mirror phenomenon among other perceptual anomalies. The *Bonn Scale for the Assessment of Basic Symptoms* (BSABS, Vollmer-Larsen et al., 2007)) represents an attempt to describe and quantify alterations of subjective experiences that may identify individuals at risk for future psychosis (McGlashan & Johannessen, 1996). Subjective experiences are named basic symptoms, and qualify as screening elements for the early detection of schizophrenia (Klosterkötter et al., 2001). In the BSABS, the item concerning "mirror-related phenomena" is included in the section covering anomalies of visual perceptual experiences, which encompasses "change in form", "change in color" and "change in other's face or body".

On the other hand, the Examination of Anomalous Self-Experiences (EASE) is a symptom checklist for semi-structured, phenomenological exploration of experiential or subjective anomalies as disorders of the basic self (Parnas et al., 2005). This scale was mainly developed for conditions in the schizophrenia spectrum and focusses only on the disorders of self (in contrast to the BSABS), with the purpose of exploring and better comprehending experiential

and behavioral manifestations. In the EASE, the mirror-related phenomena are included in "bodily experiences" but are closely related to the diminished sense of self, these phenomena are described as *"[…] a group of phenomena, which have in common an unusually frequent, and intense looking in the mirror or avoiding one's specular image or looking only occasionally but perceiving a facial change. The patients either perceive changes of their own face or they look for such changes, and therefore examine themselves in the mirror often and/or intensely. They may become surprised or frightened by what they see, and even tend to avoid mirrors because of what they see. Sometimes they look in the mirror to assure themselves of their very existence. N.B: In that case score also diminished sense of basic self".*

Below, we present examples of patients experiencing such mirror-phenomena along psychotic disorders spectrum, see figure 1.

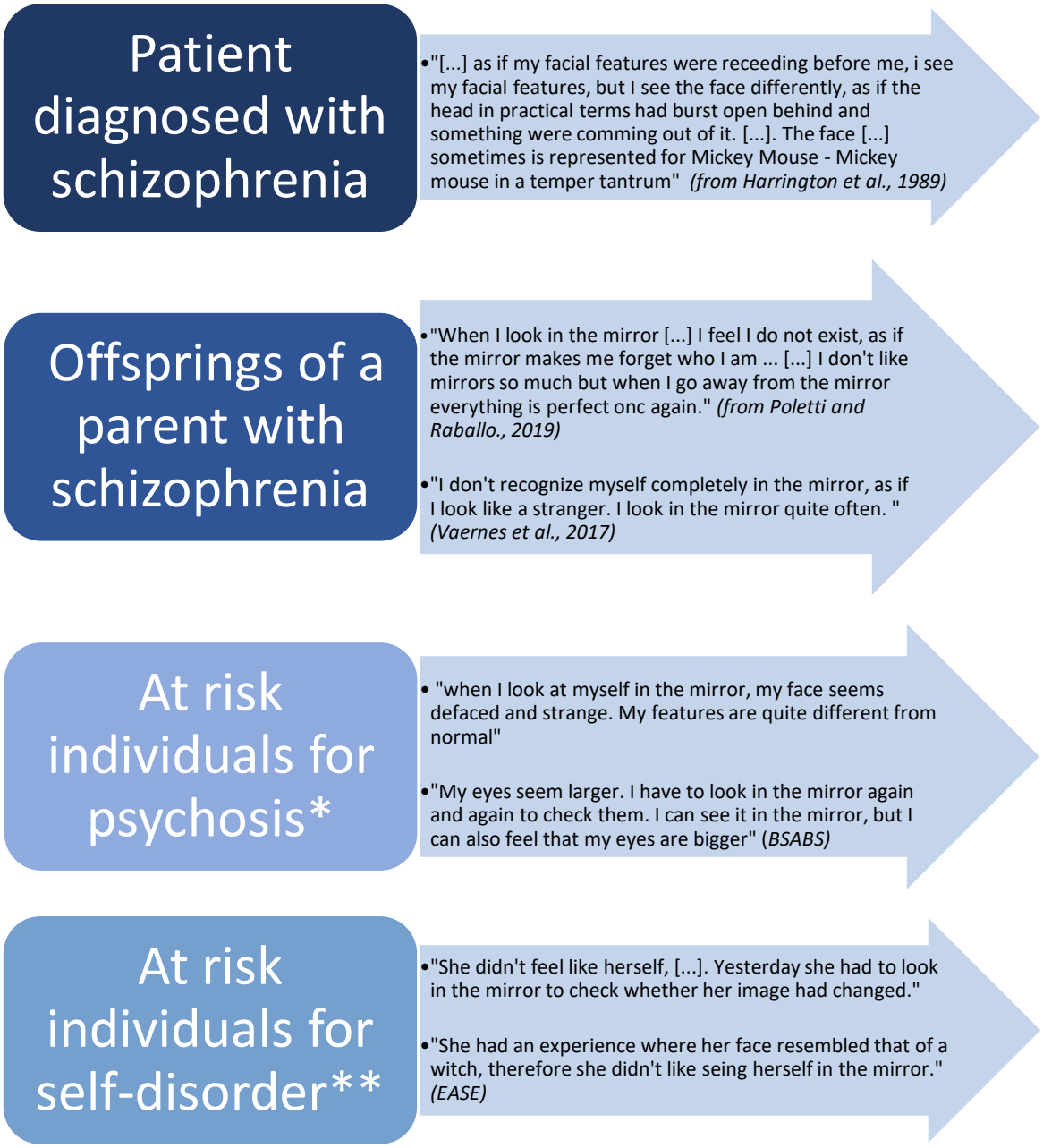


Figure 1: Description of uncanny mirror phenomenon in patients

Harrigton (1989) *provided a case study description of mirror phenomenon from a male schizophrenic patient after being asked "When you look at yourself in a mirror, has anything ever struck you particularly about your mirror image?"* ***Poletti and Raballo (2019)****, description from a 11 year-old male offspring of parent with schizophrenia.* ***Vaernes (2017),*** *description of an 18 year-old female offspring of parent with schizophrenia. *Bonn scale for*

*the assessment of Basic symptoms: examples of typical patient statements from the **BSABS** manual. ****EASE**: examples from patients evaluated with the Examination of anomalous self-experience.*

From these clinical descriptions, it is not clear which neurobiological category could explain this phenomenon. It seems that its explanation lies at the intersection between ego-pathology (such as personality psychology related to the self) and pathological perception (potentially analyzable in terms of neurocognitive approach and brain mechanisms). Hence, we propose an interdisciplinary approach compiling both self-disturbances related to the schizophrenia spectrum (notably anomalous self-experiences) and potential perceptual disturbances and their link with positive symptoms such as hallucinations.

Considering the manifestations of mirror phenomenon as subjective anomalous perceptual experiences of the self, it is firstly of importance to discuss such disturbances of the self in schizophrenia-related spectrum disorders. Subsequently, we will review the literature regarding anomalous self-experiences, and we will propose depersonalization as a potential psychological feature triggered by mirror gazing. On the other hand, the Bayesian model of perception will be reviewed as a basis for perceptual integration, and development of positive symptoms.

3.2 Schizophrenia as a disorder of the self – phenomenological approach

> "The greatest hazard of all, losing one's self, can occur very quietly in the world, as it was nothing at all. No other loss can occur so quietly; any other loss - an arm, a leg, five dollars, a wife etc.- is sure to be noticed." Soren Kirkegaard

Philosophical psychopathology (Graham & Stephens, 1994) has emerged as a new way of studying mental disorders, especially schizophrenia spectrum and depersonalization. It has long been recognized that schizophrenia involves profound transformations of the self; historically Bleuler considered a disturbed sense of self as being a core feature of the phenotype of schizophrenia (Moskowitz & Heim, 2011) and Kraepelin termed it as a "disunity of consciousness". Joseph Berze proposed that subtle alterations of self-consciousness were the primary disorder in schizophrenia. Kurt Schneider (Huber, 2002) used the idea of "loss of ego-boundaries" and Scharfeter (Scharfetter, 1980) considered delusional phenomena as compensatory relations to self-disorders. Consequently, many psychiatrists have put forward the concept of "self-disorders" at the crossroads between psychiatry, philosophy of mind (Graham, 2010; Hohwy, 2002) and phenomenology (Nelson et al., 2009; Parnas & Handest, 2003).

The sense of self can be described on three hierarchically organized but intertwined levels: the pre-reflexive, reflexive and narrative self (Damasio, 2010; Parnas, 2011). The most basic sense of self is the *implicit*, pre-reflexive egocentricity and is built in the subjective experience itself (i.e. the bodily self, the automated self that we do not question). The *reflexive* self is defined by explicit awareness of an "I" that is stable over time (i.e. self-awareness, we recognize that

we exist as a "I"). And, the *narrative* self is the experience of the self as having characteristics and personality (i.e. self-image, self-esteem, social self, which characterize the evolving story of the self).

A consensual literature proposes that disturbance of the minimal self (implicit) is at the core of the disorder (Parnas, 2011; Sass, 2001). The ipseity-disturbance model (IDM) proposed by Sass and Parnas explains instability of the minimal self with two interconnected characteristics: hyper reflexivity and diminished self-affection. Hyper reflexivity refers to heightened awareness of aspects of experience that are normally implicit (i.e. exaggerated and alienating forms of self-consciousness, implicit aspects of one's body is experienced in an explicit way such as awareness of the act of breathing or sensations when walking). Whereas diminished self-affection is described as a weaken sense of existing as a subject of awareness (i.e. diminished self-presence and identity, feeling of not belonging to the world, fading first-person perspective, see (Henriksen & Parnas, 2012) for a clinical description). These processes disrupt a person's "grip" or "hold" on the perceptual field of awareness and manifest in a range of anomalous subjective experiences. ASEs are typically observable in the prodromal phase before the emergence of psychotic symptoms (Moller & Husby, 2000; Parnas et al., 2011a), and in some individuals, they are already present in childhood and adolescence (Nelson et al., 2014a).

An updated neuro-phenomenological model of self-disorders in schizophrenia was proposed by Sass and Borda in 2015, attempting to integrate schizophrenic subjectivities with neurodevelopmental findings (Sass & Borda, 2015). They suggested that basic self-disorders were sustained by both primary and secondary factors. Primary factors would reflect early childhood disturbances in neurodevelopment (disturbances in sensorimotor functions and perceptual integration necessary for typical experience of consciousness, existence and feelings

(Damasio, 2010)). While secondary factors were considered as defensive-compensatory reactions to primary factors and other stressors (i.e. trauma). They might occur early in the life course, but they tend to get more pronounced during adolescence and early adulthood. According to Sass and Borda, ASEs in other disorders (notably depersonalization disorders), correspond closely to those in schizophrenia, however they are only secondary and defensive in nature. They proposed that, during childhood, schizophrenia patients might predominantly display primary phenomenological abnormalities (i.e. perceptual disturbances affecting perceptual organization), whilst secondary alterations (i.e. secondary hyper reflexivity and diminished self-presence) appear in adolescence and early adulthood, potentially triggering a first psychotic episode. They postulated that primary and secondary features co-occur to some extent, and schizophrenia patients may differ according to the relative contribution of each features.

3.3 Anomalous self-experiences along the schizophrenia spectrum

As reviewed above, advocates of the phenomenological current believe that schizophrenia is a self-disorder, of which the trajectory starts as early as childhood and precedes the onset of clinical symptoms. Thus, the basic self should also be relatively disturbed in individuals at heightened risk of developing psychotic disorders, who are still symptom-free. The aim of the present thesis is to understand the relationship between self-disturbances and psychometric increased risk for psychotic disorders (schizotypy). Anomalous self-experiences (ASE) belong to the wider classification of anomalous experiences, encompassing two other main categories: *anomalous perceptual experiences* (distortions of sensory events in the different domains: auditory, visual, touch, and taste); and *anomalous delusional beliefs*, experiencing unusual thoughts or beliefs. ASEs in the sense that the subject feels s/he is not real (distortions in experience of the self and being), include forms of depersonalization, distortions of first-person perspective, disturbed self/other and self-world boundaries, diminished sense of existing as a bodily subject and a diminished sense of coherence in fundamental features of self (i.e. identity confusion, Parnas et al., 2005). In table 2, one can find the different domains of ASEs with their features and corresponding examples. Research suggest that these ASEs precede "surface level" anomalous perceptual experiences such as hallucinations (Nelson et al., 2014) and anomalous delusional beliefs might develop from anomalous experiences (Fletcher & Frith, 2009; Freeman et al., 2002; Garety et al., 2001). When transitioning to full blown psychosis, anomalies of self-experiences are expressed by the emergence of delusions, hallucinations or passivity experiences (Scharfetter, 1980).

Domains	Features	Examples
Alterations of stream of consciousness	Disruption of the implicit sense of 'mineness' of mental content Thoughts take an almost autonomous and anonymous identity, they are no longer a lived aspect of subjectivity	Interruption in the course of thoughts, thoughts are experienced as uncontrolled, and their content is meaningless to the person
Altered sense of presence	Disturbed presence is characterised by a sense of self alienated from itself	Depersonalization, derealization, sense of inner void. The individual does not own his/her experience. Gap between self and experience of the outside world. Deficiency in grasping obvious meanings.
Alterations of the experienced body	Bodily basic symptoms: impaired bodily sensations Experiential distance between sense of self and bodily experience	Part of the body appear as changed, or appear strange, alien or lifeless Patients lose their ability to perceive their own body.
Impaired Self-demarcation	Weaken self-other and self/world boundaries	Confusion of boundaries between self and others, sense of passivity in relation to the world, presence and contact of others experienced as threatening
Existential reorientation	Solipsism Preocupation with philosophical, metaphysical themes.	Individual live as a single subject of the world. Impressions of centrality or the mind dependence of the world: external events are addressed to the patient.

Table 2: Table of the different domains of basic self-disturbances, or ASEs

This table was adapted from Nelson & Raballo, 'Basic self-disturbances in the schizophrenia spectrum: taking stock and moving forward'. 2015. Psychopathology. DOI: 10.1159/000437211

Studies showed that minimal self-disturbances are more prominent in schizophrenia than in psychotic disorders outside the schizophrenia spectrum (Haug et al., 2012; Parnas et al., 2003). Moreover, they were found to strongly predict future onset of schizophrenia spectrum disorders in individuals at high risk for psychosis (Nelson et al., 2012) as well as in non-psychotic clinical patients (Parnas et al., 2011), in addition to being equally observable in schizotypal personality disorder (Handest & Parnas, 2005). More precisely, Nelson and colleagues showed that levels of self-disturbances were significantly higher in UHR samples when compared to healthy controls, and the total self-disturbances score predicted transition to psychosis (Nelson et al., 2012). A follow-up study of five years suggested that self-disturbances represent a strong predictor of schizophrenia spectrum diagnosis in individuals without psychotic conditions (Parnas et al., 2011b). Raballo and Parnas (Raballo et al., 2011) demonstrated that self-

disturbances were incrementally present in grouping of family members without mental illness, with no mental illness but that of schizotypal traits and schizotypal personality disorders.

Thus, converging empirical evidence from the phenomenological account indicates that certain anomalous subjective experiences in the form of non-psychotic disturbances of the basic sense of self might represent a vulnerability marker for schizophrenia spectrum disorders. In schizophrenia they are believed to underpin and generate positive, negative and disorganized symptoms (Parnas & Handest, 2003). These disturbances are distortions of the fundamental levels of consciousness, and later they can – through personal conscious attribution – develop into delusions or hallucinations. Consequently, ASEs in phenomenological theories are considered as strong phenotypic markers of vulnerability to schizophrenia, and the identification of ASEs, notably through the EASE, has been suggested for identification of individuals at higher risk for psychosis and self-disorders.

However, the specificity of ASEs is not consensually settled, ASEs are not restricted to the schizophrenia spectrum and also occur in non-psychotic state such as depersonalization (Værnes et al., 2018), thus the following paragraph details the account of depersonalization and its link with the mirror phenomenon.

3.4 Depersonalization as an ASE triggered by mirror gazing

Depersonalization is usually defined in its basic form as non-psychotic or near-psychotic and described as a diagnosis criteria of schizotypal personality disorder in the DSM-V and the ICD-10. Depersonalization disorder (accompanied with severe depersonalization and functional impairment) is classified with four other criteria as one of the Dissociative disorders in the DSM-IV, but as a neurotic condition in the ICD-10. It is usually characterized by feelings of

unreality and detachment with the self (Holmes et al., 2005), which clinically represent the depersonalization disorder (DPD). An alternative view proposes to conceptualize depersonalization as a syndrome rather than a symptom, which is not restricted to feelings of unreality and detachment and encompass various symptoms, including emotional numbing, derealization (detachment from the world), feelings of disembodiment (no body ownership or agency feeling), and anomalous subjective recall (being unable to ascertain that an event actually happened) (Sierra & David, 2011). In another study, Simeon and colleagues (Simeon et al., 2008) defined five factors instead of four: numbing, unreality of self (detachment from the physical body, mind, actions and thoughts), perceptual alterations (encompassing visual, tactile and somatosensory modalities), reality of surrounding (which correspond to the DSM-IV description of derealization) and temporal disintegration (disturbances in subjective experience of time and imagery). One factor is of particular interest within the context of this thesis, the perceptual alteration factor, as it includes parts of the body perceived as alien, strange, dislocated or not existing, and may be accompanied by perceptual changes when mirror gazing (the mirror phenomenon). Moreover, Simeon and colleagues (Simeon et al., 2000) assessed the positron emission tomography (PET) brain correlates in subjects with depersonalization disorder, and found altered activation in sensory association cortical areas and occipital cortex, representing visual and somatosensory pathways, as well as in areas responsible for an integrated body schema. These results suggest that the phenomenology of depersonalization disorder might represent a dissociative disorder in which there is a failure to integrate perception of the sense of self.

Hence, although there is poor agreement on the constituent symptoms of depersonalization, the perceptual alteration factor may relate to what is experienced during mirror gazing, as patients have reported seeing in the specular image other identities than themselves (such as monsters and other people). The depersonalization theoretical account led us to think of ASEs as state

phenomena that might be triggered by mirror gazing as opposed to markers for psychosis as described by the phenomenological theories. Experiments of perturbation of such self-perception have been described, including autoscopic hallucinations, heautoscopy (perceiving one's own image in front of oneself), and out-of-body experiences, leading to disturbances in the perception of body self (sustained by disturbances in integration of visual, tactile and proprioceptive information). Consequently, to further understand the phenomenon of depersonalization seemingly triggered during mirror gazing, an alternative experimental methodology can be used to induce transient psychotic-like experiences in individuals expressing schizotypy traits. In this context a potential direction would be sensory deprivation, which has been shown to mimic the most closely clinical psychotic symptoms. Below, we will present a brief overview of sensory deprivation studies that have been used to induce depersonalization-like symptoms, notably in the field of visual perceptual illusions.

3.5 An alternative model of psychosis: sensory deprivation to induce anomalous perceptual states

Sensory deprivation represents a good candidate to provide a model for psychosis in psychiatrically healthy individuals without the administration of psychoactive drugs (Rosenzweig, 1959), and helps us bridge the gap between the laboratory and the clinic. Historically, the advent of sensory deprivation investigation began in the 1950's and 1960's with changes in experiences and cognition in subjects who endured extended periods of sensory and social isolation such as war prisoners, these changes were found to be comparable to those induced by pharmacological interventions (Luby, 1959). A limited pool of studies has investigated the effects of sensory deprivation in patients with schizophrenia and schizotypy, and results are inconsistent. Some studies have shown that psychiatric patients reported

hallucination while being secluded (Richardson, 1987), while other studies suggested that schizophrenia patients tolerated sensory deprivation reporting less intense hallucinations when sensation were restricted (Cohen et al., 1959). In one study, interested in psychosis proneness, McCreery and Claridge (McCreery & Claridge, 1996) observed that high schizotypy individuals reported anomalous self-experiences during sensory deprivation.

Only a handful of studies used sensory deprivation to successfully induce visual hallucinatory phenomena in healthy individuals. In student volunteers, experimental isolation and sensory deprivation led to difficulties in concentration, affective disturbances and vivid hallucinations (notably visual) and delusions (Bexton et al., 1954). In Bexton's study, twenty-two males were placed in cubicles for 2-3 days under reduced sensory variation, they noted disturbances in visual perception when coming out of the cubicle. A combination of auditory and visual deprivation by the use of white noise in headphones, and white Ganzfeld field goggles was applied in participants for 30 minutes (Lloyd et al., 2012). Participants reported spontaneous visual, bodily and auditory sensations, and those who were more prone to hallucinations, as measured by the Revised Hallucination Scale (RHS), reported more distinct perceptions. Another longer experiment was conducted by blindfolding for 96 hours per day 13 healthy individuals (Merabet et al., 2004). 10 (77%) out of the 13 participants reported visual hallucinations varying in duration, onset and content. Participants started to experience hallucinations between the first and second day of blindfolding and they did not have control over their emergence. They described flashing lights, landscapes and faces among other visual apparitions. Mason and Brady (Mason & Brady, 2009) investigated perceptual disturbances after 15 minutes of complete visual and auditive isolation. 19 healthy participants were included in this study, divided into hallucination proneness (n=10) and low hallucination proneness (n=9), as measured with the RHS, and they used the anechoic chamber to induce sensory deprivation. The anechoic chamber consists in a room sound-proof and plunged in total

darkness. Paranoia, anhedonia and perceptual disturbances were experienced by both groups, however, the hallucination-prone group reported more perceptual disturbances. Altogether, these studies using several methodologies showed that sensory deprivation is a successful technique to induce hallucinations-like phenomena in healthy individuals.

We posit that reproducing the mirror phenomenon in typically developing individuals will deepen the knowledge on this phenomenon and its manifestations. The aforementioned observations of mirror anomalous self-experiences resulted from either case studies or semi-structured interviews in clinical population, notably used in the detection of high-risk state. Whilst the use of high-risk model is emerging and a fruitful contribution to the field of psychotic disorders, investigation using experimental paradigms in these clinical sample is hardly feasible. Caveats in the existing literature call for the need of alternative experimental methodology to induce transient psychotic-like perceptions in individuals with schizotypy traits. In this context, sensory deprivation will be employed. Below we review the use of mirror gazing, from ancient times to contemporary standardized paradigms, to induce a sensory deprivation context leading to visual illusions ranging from perception of light and shapes to subjective strange-face apparitions and phenomena of depersonalization. Subsequently, the mirror gazing paradigm will be integrated in the Bayesian framework of emergence of anomalous perceptual experiences.

3.6 From Psychomanteum to Mirror gazing task

Literature on mirror-gazing describes how mirrors, crystals, still liquids and other reflective surfaces have been used throughout history for the purpose of observing spontaneous apparitions. For instance, shamanic mirror-gazing traditions were found in Siberia, Madagascar, North America and parts of Africa. Inspired by the ancient Greeks and their

"oracle of the dead", the psychomanteum was popularized by Raymond Moody (Moody, 1976), and described as a small, enclosed area, set up with a large mirror on one wall where people would come and gaze deeply in the mirror to connect with deceased relatives. Moody interviewed about 300 individuals about their experiences; a quarter of participants encountered a deceased person and he noted that the experience often began with appearance of mist or smoke accompanied by colors, lights or shapes.

Turning to more traditional studies of mirror-gazing, Caputo (Caputo, 2010a, 2010b) proposed a standardized task to study perceptual modifications of the specular image, the Mirror Gazing Task (MGT). Participants are seated in front of mirror in a room dimly lit by only a lamp and their task was to gaze at their own reflected face within the mirror. In this first study of 2010, 50 healthy young adults described what they perceived in the mirror; 66% of them experienced deformations of their own faces; 18% saw a parent's face with traits changed, of whom 8% were still alive and 10% were deceased; 28% reported seeing an unknown person (archetypal face, i.e. child, old person); 18% described an animal face and 48% fantastical or monstrous being.

In another study (Caputo et al., 2012), the authors compared 22 patients diagnosed with schizophrenia and 22 healthy controls, providing evidence that schizophrenic patients experienced more intense strange-face apparitions than healthy individuals. Furthermore, reality of apparitions was stronger in schizophrenics, as in many patients were convinced that the strange apparitions they experienced were real. Subsequently, Fonseca-Pedrero and colleagues (Fonseca-Pedrero, et al., 2015) validated the MGT in a community sample of 110 adolescents, and reported that those who experienced dissociation of self-identity presented higher scores on the schizotypal personality questionnaire, suggesting an initial association between schizotypy and proneness to experimentally-induced ASE during adolescence. They also showed that 20% of the sample reported slight change of light or color and 45.5% own

face deformation. In terms of strange face vision, 27.27% reported seeing another identity, while 7.27% reported non-human vision. This study initiated the idea that MGT, when used to experimentally induce self-face illusions, could serve as a proxy measure to test the proneness to ASE in developmental periods.

The theoretical account of Bayesian model of perception reinforces the idea that sensory deprivation is a useful paradigm to explore and explain the mechanisms of emergence of anomalous perceptual experiences as triggered by the mirror gazing task.

3.7 A Bayesian model of anomalous perceptual experiences: your perception depends on your perspective

> "Instead of saying that an hallucination is a false exterior percept, one should say that the external percept is a true hallucination". Hippolyte Taine, 1870.

A Bayesian model of information processing was proposed by Corlett (Corlett et al., 2009a) and Fletcher and Frith (Fletcher & Frith, 2009a), suggesting that experimental interventions that induce psychotic symptoms affect the interaction between an individual's predictions about the world and the sensory input encountered. Under typical circumstances, the interaction shapes learning and experience, however, when disrupted it can result in hallucinations and delusional beliefs as seen in positive symptoms of psychosis. This Bayesian model conceptualized information processing in terms of sensory current input (bottom-up or sensory predictions) and of prior beliefs/expectancies (top-down/cognitive predictions). A mismatch appearing between these endogenous and sensory predictions leads to the error prediction

signal, which in turn updates inferences that one has about the world and generates new predictions for the future. The present model suggests that the expression of positive symptoms in psychosis (i.e. hallucinations) result from a weakened bottom-up signaling. Therefore, the strong endogenous priors (expectancies) might create the experience of a percept without a basis in external reality as a consequence of absence of strong reliable bottom-up sensory signals. In the context of sensory deprivation, it is suggested that healthy individuals experience a lack of bottom-up sensory stimulation, thus the predictions of higher brain regions are violated. Furthermore, sensory deprivation is never complete, and there exist baseline noisy bottom-up signals which compete with strong priors that are normally acting upon stronger signals. Finally, the resulting prediction errors and noisy signals are treated as genuine inputs, leading to subsequent illusions (Corlett et al., 2009).

In the context of this Bayesian model, in the case of mirror gazing under low light conditions, we reproduced a sensory deprived environment, representing a relative lack of reliable bottom-up sensory simulation. Sensory deprivation is not fully complete with some low-level noisy bottom-up signal persisting, as one could see facial features, but can be considered impaired. However, top-down processes remain unaffected. Thus, prediction errors occur as a result of un-impaired top-down endogenous signals attempting to impose some meaningful interpretation of the sensory-deprived bottom-up input, resulting in visual illusions (uncanny apparitions in the mirror), see figure 2.

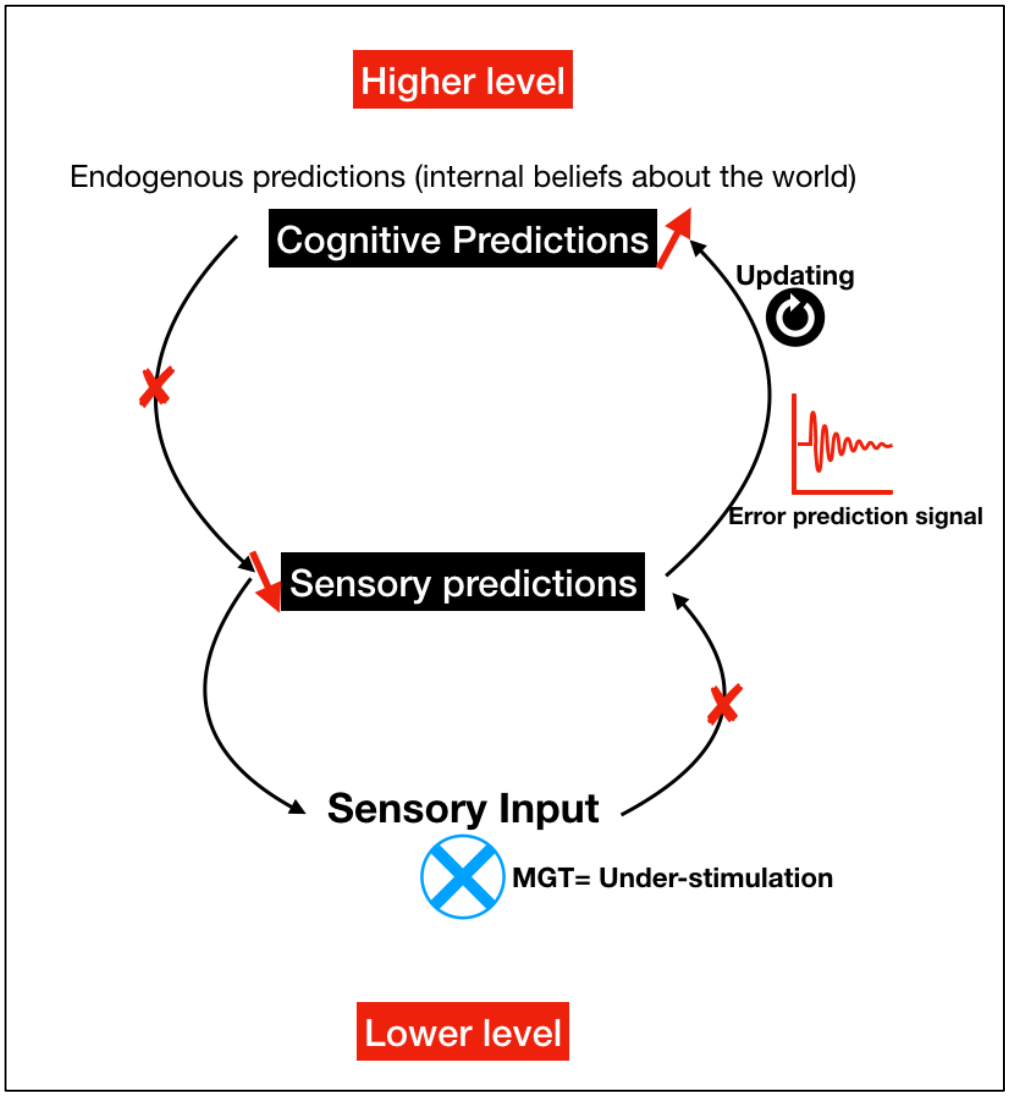


Figure 2: The Bayesian model of emergence of apparitions in the context of sensory deprivation using the MGT.

The set-up induces sensory visual deprivation, leading to a mismatch between sensory input and endogenous priors that one has about his/her own face. Subsequently, the error prediction signal occurs as a result of un-impaired cognitive predictions attempting to impose meaningful interpretation on the bottom-up sensory input.

The previous passages have shown that ASEs are closely related to the spectrum of psychosis disorders, and that we can induce a specific subtype of ASEs, the mirror phenomenon-like state in the general population through sensory deprivation, with the mirror-gazing task. The Bayesian theory allows us to hypothesize a model of apparition of such depersonalization-like phenomena, proposing that our brain entertains a predictive model of the environment, assuming that predictions are implemented across hierarchical levels. We believe that prediction errors are generated when a mismatch happens between incoming sensory input and prior beliefs, leading to an emergence of anomalous self-experiences in the context of the MGT. Therefore, two distinct accounts which might not be mutually exclusive, will help disentangling the neural correlates of experimentally induced ASEs in the context of the present thesis. The first will integrate neuroimaging findings of self-referential processing and secondly, we will review studies investigating the mechanisms of emergence of hallucinations (notably visual).

3.8 The dynamic neural model of self

Despite the large array of structural neuroimaging investigations, the neurobiological substrate of basic self-disturbances is unknown. Below, we present recent evidence that points towards brain function and structural alterations underlying the basic self. Similar to the Bayesian hierarchical model of perception, the different aspects of self can additionally be divided in hierarchical dynamic processes sustained by specific brain regions.

In a meta-analysis, Northoff and colleagues (Northoff et al., 2006) proposed a model to describe the cortical localization of the different concepts of self. Those concepts are related to sensory, self-referential and higher order processing, each being underpinned by their respective cortical regions (sensory, medial and lateral cortices). The proto or bodily self refers to pre-reflective sensory processing, the ‘core’ self refers to self-referential processing and

‘autobiographical’ self refers to higher order cognitive processing. Damasio, characterized the core self as a transient neural representation that alters from moment to moment, as internal bodily states are integrated with external stimuli. The ‘autobiographical self’ integrates to maintain a dynamic self-representation over time. The cingulate network – with its afferent and efferent connections traversing cognitive, motor, somatosensory and visceral systems – was identified as sustaining the ‘core self’. Thus, cortical midline structures are viewed as playing an intermediate role between sensory and higher order cognitive processes. Northoff identified three clusters within the cortical midline structures, constantly recruited in self-related tasks in healthy volunteers: 1) pre- and sub-genual anterior cingulate cortex (ACC)/ventromedial prefrontal cortex, 2) supra-genual ACC/dorsomedial prefrontal cortex and 3) posterior cingulate cortex (PCC). Collectively, these areas play a role in monitoring (ACC), integration of self-referential stimuli (PCC), and in the evaluation and representation (medial prefrontal cortex (MPC). This dynamic model is subject to top-down and bottom-up modulations. We could hypothesize, based on the principles sustaining the Bayesian model, that sensory processing of the self is altered by sensory deprivation, sending mixed signals to the self-referential processing center, from which higher order processing related to prior knowledge about oneself mismatch with the self-referential processing of the self. Subsequently, the top-down updated flow would attempt to impose meaningful representation of one’s self, resulting in altered perception of one’s own face.

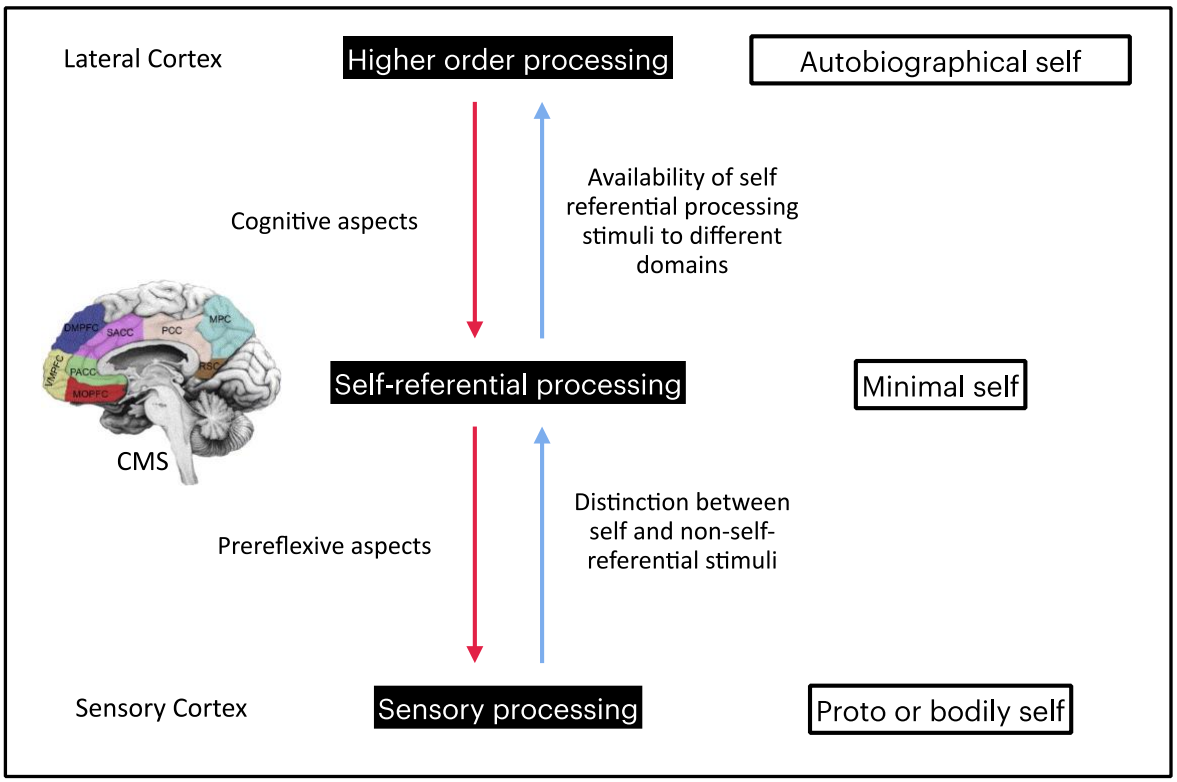


Figure 3: The neural dynamic model of self

This model and the schematization of Cortical Midline Structures (CMS) were reproduced and adapted from Northoff et al., 2006, Neuroimage, 10.1016/j.neuroimage.2005.12.002.

The schema of CMS structure includes MOFC= medial orbital prefrontal cortex, VMPFC= ventromedial prefrontal cortex, PACC= pre and subgenual anterior cingulate cortex, SACC= supragenual ACC, DMPFC= dorsomedial prefrontal cortex, RSC= retrospenial cortex. The global schema represents the relationship between cortical regions and different concept of the self. Sensory, self-referential and higher order processing are sustained by their respective cortical localization. Arrows indicate bottom-up (Blue), and top-down (red) modulation.

The extent to which alterations of cortical midline structure regions relate to basic self-disturbances, notably to task-induced ASEs, has yet to be investigated. Investigating these features could improve the detection and prediction of neural patterns corresponding to ASEs.

Thus, another account that could inform research on neural patterns of ASEs would be the neural mechanisms of hallucinations, as observed on the clinical side of the spectrum.

3.9 Neural mechanisms of hallucinations

Although a number of studies have explored the neural underpinnings of hallucinatory experiences, there is a limited consensus, which could be explained by the challenge of capturing spontaneous hallucinatory experience in the scanner. In this section we will review the account of functional neuroimaging studies with a focus on visual hallucinations and propose the model developed by Allen and colleagues (Allen et al., 2008) of bottom-up and top-down processes leading to erroneous percepts. This meta-analysis encompasses a large amount of studies from which the most reproduced findings suggest that, in addition to sensory cortices, dysfunctions in prefrontal, cingulate and subcortical regions contribute to hallucinations. They summarized that the hallucinating brain is characterized by reductions of gray matter volumes in temporal cortices, increased activation in subcortical structures, decreased control of the dorsolateral prefrontal cortex, impaired activation of emotional centers of attention (ventral anterior cingulate) and attenuated activation of dorsal anterior cingulate and cerebellum involved in monitoring processes. Their model hypothesizes bottom-up dysfunctions due to hyperactivation in secondary sensory cortices leading to vivid perceptions while no sensory stimuli is incoming. The weakened top-down control associated with ventral anterior cingulate, prefrontal and cerebellum activity attenuation may lead to the experience of externality through impaired monitoring processes. In parallel, hyperactivity of cortical and subcortical regions regulating the emotions (cingulate, orbitofrontal, para hippocampus) sustain the affective dimension of the hallucination.

Although interesting, this model requires further investigation, and more research is needed concerning visual hallucinations. Moreover, the recruitment of patients in studies included in

the meta-analysis was not consistent and not all studies controlled for the effect of medication. Hence, the neural mechanisms underlying hallucinatory experiences remains ambiguous, and there is still a lack of unified theories accounting for hallucinations in multiple modalities. Understanding the neural mechanism of task-induced visual illusion in the general population has the potential of providing a groundwork, from which one could get insights on the mechanism of apparitions of visual hallucinations.

To summarize this section on the concept of anomalous self-experiences, we showed that anomalous self-experiences are related to subtle disturbances of the self-observable along the spectrum of psychotic disorders. We were more precisely interested in a specific type of ASEs clinical manifestations, the mirror phenomena. To understand this phenomenon, we proposed that the duality of trait and state approach would help us answer our main hypothesis that schizotypal personality trait might provide a basis for the proneness of expressing transient sub-clinical states, such as depersonalization phenomena. We proposed an alternative way of studying these phenomena which is to actually provoke them in healthy individuals, and that this could be reached with sensory deprivation methodologies. We reviewed the diverse techniques of visual sensory deprivation and introduced the mirror gazing task that is used in the present PhD thesis. The Bayesian model of perception processing provided an exciting framework to hypothesize the mechanisms of emergence of such unusual perceptual experiences. The dynamic model of the integration of different concepts of the self-paralleled and completed the Bayesian model of perception, allowing for new hypothesis concerning the emergence of perceptual anomalous self-experiences. Ultimately, the dynamic model of pathological hallucinations and its underlying neural correlates will allow us to draw differences and similarities with the neural mechanisms of apparitions of experimentally induced ASEs.

The main caveats identified in the reviewed literature are, firstly, that we have no knowledge concerning the developmental trajectory of proneness to ASEs in the general population, and, secondly, very few studies have investigated the relationship between ASEs and traits schizotypy and further research is needed to elucidate whether schizotypy traits potentialize the proneness to ASEs. Finally, evidence points toward early visual abnormalities that trigger a cascade of disturbed neural activity creating distortions in one's experience. However, it is unclear how basic visual and complex functions of the brain contribute to visual misperception.

4. Rationale of the project

This thesis aims to achieve a better understanding of the evolution – during non-clinical phases – of the risk to develop psychotic disorders involving a duality trait-state. Our first goal is to broaden the knowledge on cerebral morphology correlates of schizotypal personality traits. By means of a newly developed longitudinal statistical procedure, we could investigate developmental trajectories of cortical and subcortical structures along adolescence. Secondly, we wish to introduce an experimental procedure inducing visual ASEs and evaluate the prevalence, persistence and distribution of ASEs in the general population. Lastly, we wish to uncover the neurobiological underpinning of these task-induced ASEs that could inform neural mechanisms of visual hallucinations.

Ultimately, we wish to bridge the gap between schizotypal personality traits and manifestations of self-disturbances in the general population, to reconcile the two accounts of the literature – the contemporary concept of schizotypy and the role of the dimension of the self, put forward by the phenomenologists, which both have their place in the understanding of psychotic disorders. To reach such a goal, we clarify the effect of transient sensory deprivation (using the MGT) on individuals who vary in their degree of proneness to ASEs (schizotypy). We ask ourselves whether highly schizotypal individuals are more likely to erroneously process inner previous beliefs when in conditions of sensory deprivation, in which external stimuli are absent or minimal, leading to anomalous self-experiences phenomena?

This work carries the potential to impact the field of research on early detection of psychotic disorders by providing further insights on these two distal predictors: schizotypy and

anomalous experiences of the self. Studying these constructs and understanding their dynamic relationship in typically developing individuals (and more importantly during adolescence) will help understand maladaptive development and might trigger some new ideas for early prevention of psychotic disorders. Furthermore, the strength of this project resides in the longitudinal perspective, as to date, only some research has provided developmental measures during adolescence, including measures of schizotypy and anomalous self-perceptions. This project uses an experimental set-up of sensory deprivation and state-of-the-art neuroimaging techniques to characterize how brain abnormalities could lead to self-related visual distortions in psychotic disorders. Predicting neural activations patterns during the course of task-induced self-illusions, might clarify brain mechanisms at stake in the development of visual hallucinations observed in clinical samples.

Chapter II

Methodology

This project encompasses diverse methodologies, from behavioral to neuroimaging studies. In this chapter we detail the basis of task, questionnaires and magnetic resonance imaging (MRI) measures that will be used in the studies that will be presented in the empirical section.

1. Measuring schizotypy

A wide variety of self-reported measures have been used to assess schizotypal features. The rationale for their use include the potential to identify individuals at risk for transition to psychosis, identify events that precede the illness (including potential protective factors), and enable the analysis of construct without the confounds of illness (Chapman et al., 1995). These self-reported questionnaires can be divided in two main categories: those measuring specific dimension of symptoms, such as positive symptoms (i.e. Perceptual Aberration scale, Peters et al Delusional Inventory) or negative symptoms (i.e. Social Anhedonia Scale or Physical Anhedonia Scale), and those encompassing the multidimensional features of schizotypy (i.e. Schizotypal Personality Questionnaire).

In this project we chose the Schizotypal Personality Questionnaire (SPQ) as the main instrument to measure schizotypy (see appendix 1). The rationale was that it is an instrument that could measure schizotypal features as attenuated versions of schizophrenia symptoms. The SPQ was designed based on DSM-III-R clinical definition of schizotypal personality disorders (SPD: American Psychiatric Association, 1984). It consists of 74 dichotomic items (Yes/No

answers) and is self-administered. It contained 3 dimensions (positive, negative and disorganized) and 9 subscales: unusual perceptual experiences, odd/magical beliefs/thinking, ideas of reference, and suspiciousness, loading on the positive dimension, excessive social anxiety, no close friends, constricted affect, and suspiciousness (double loading) loading on the negative dimension, odd behavior, and odd speech, loading on the disorganized dimension (Raine, 1991). A shortened version with 22 items has also been developed, the SPQ-brief (Raine & Benishay, 1995), and this shortened version was adapted for children, the SPQ-C (Liu et al., 2019). The three factor structure of the SPQ has been replicated in many different samples: undergraduates (Gruzelier, 1996; Raine et al., 1994b), adults participants (Badcock & Dragović, 2006), adolescents (Fonseca-Pedrero et al., 2018; Fossati et al., 2003b), psychiatric patients (Rossi & Daneluzzo, 2002; Vollema & Hoijtink, 2000), patients with personality disorders (see (Adrian Raine, 2006) for a review). The SPQ present relatively high convergent validity with psychosis-proneness measures, such as with the Chapman scales (Wuthrich & Bates, 2006). Other studies have observed overlap between schizotypal features as measured with the SPQ and prodromal symptoms (67% of schizotypal diagnosed patients met the criteria for prodromal symptoms, and 26% of prodromal patients reached the criteria for SPD, (Wood et al., 2008)). To sum up, the SPQ covers a wide range of schizotypal features, whilst presenting good psychometric properties including reliability and convergent validity, which makes it a reliable candidate.

2. Measuring anomalous self-experiences

There are many different self-reports and interview-based instruments available in the literature to measure ASEs (i.e. EASE, BSABS as mentioned in the introduction, section 3.5). These available measures consist of symptom checklists comprising different domains, such as in the

example of the EASE: cognition and stream of consciousness, self-awareness and presence, bodily experience, transitivism and demarcation, and existential reorientation. They encompass a wide range of ASEs.

However, since self-experiences aberrations appear to occur spontaneously, self-report and interview-based assessment might not be optimal to quantify subtle anomalies in real time. Although difficult to objectively quantify, bodily self-aberrations have been efficiently studied using virtual reality paradigm such as the rubber hand illusion (Thakkar et al., 2011), the Pinocchio illusion (Burrack & Brugger, 2005), and the full body illusion (Blanke & Metzinger, 2009). Virtual reality is an immersive technology that aims at substituting sensory input about one's environment. This method enables scientists to create illusions of bodily-self reference and ownership. During these types of illusions, individuals can genuinely feel outside of their bodies or embodied in another (Aspell et al., 2009; Blanke, 2012; Blanke & Metzinger, 2009). Inspired by this technology, but with the will of using an MRI scanner, we used another visual self-recognition paradigm inducing ASEs-like illusions, the Mirror Gazing Task (Caputo, 2010; Fonseca-Pedrero et al., 2015), which was mentioned above.

The MGT was conducted in a darkened room, a parcel of which (2 x 3 m) was dedicated to isolate the subject seated in front of a mirror, in between a white wall and a white screen. A large mirror (0.5 x 0.5 m) was propped on the upper part of the computer desk, held on a tripod, and a keyboard was placed on the lower sliding part of the computer desk. Participants sat so that their eyes were at a distance of 0.4 m in front of the mirror. The room was only illuminated with a halogen bulb (12V, 20W, equivalent to a measure at the eye level of 0.8 lux, or 0.2 $cd.m^{-2}$), placed 1.2 m behind the participant, with the bulb facing the floor. This set up provided diffuse, indirect lighting over the room, allowing fine facial features to be distinguished in

detail whereas colors were attenuated. An experimenter seated behind the screen conducted the MGT.

Concerning the recording of the event-related responses, the experimenter explained the use of the keyboard: "*During the 10 minutes while you are looking at yourself in the mirror and staring at your eyes, you may or may not notice changes on your face. If you notice a change then press the button and hold it down for as long as the change lasts. If you do not notice any changes then do not press the button*". The experimenter made sure the participant understood the instructions and further clarified any ambiguous points before the task began. After the end of the task, a post-MGT questionnaire was filled asking the following questions among others, see appendix 2: *"During the task, have you notice a change in light, color or contrast? If yes describe",* "Did you see another person in the mirror? If yes, describe", "Please provide a list of all *types of modifications you noticed during the task".* In addition, participants answered three five-point Likert-type scale sentences ranging from 'never' to 'very often': *"How often did you notice anything strange?", "How often did it seem real?", "How often did you see another person in the mirror?".*

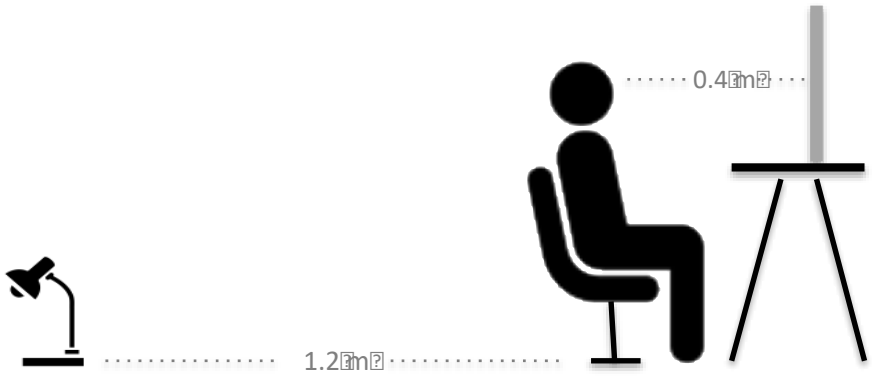


Figure 4: Set up of the mirror gazing task, adapted from Caputo et al., 2010

3. Neuroimaging methods to study brain correlates

Today, the MRI represents a non-invasive method to investigate brain function and structure. Even though several brain functions can be localized on the cortical surface of the brain, complex cognitive processes rely on the cooperation of numerous brain regions (A. Evans & He, 2015). Thus, as we are interested in different processes, in the present project we will use two different types of MRI; structural MRI and functional MRI (within which we defined two sub-types: task-related functional-MRI, and resting state functional-MRI).

3.1 Basic principles of structural MRI for human brain development

Briefly, MRI is based on the electromagnetic activity of atomic nuclei (Bitar et al., 2006) which are made of protons and neutrons. In structural imaging, hydrogen nuclei from water molecules are used in order to form the MRI signal (Pooley, 2005). The hydrogen proton is charged positively and acts as a tiny magnet. In this context we are interested in T1-weighted images that best depict anatomy, where hydrogen protons are visualized.

T1-weigthed images are used to assess the physical integrity of grey (GM) and white matter (WM), and there are several approaches to examine the size and shape of brain structures, mainly arranged around 2 modalities: morphometry-related analyses, focusing on GM or WM volumes; and surface-based approaches, considering cortical thickness or cortical curvature.

In the project we concentrated on cortical thickness and subcortical structures volumes. Surface-based analysis allows morphometric measures obtained with cortical surfaces. The cortex is delimited by the boundary between cortical GM and cortical WM, as well as the boundary between GM and cerebrospinal fluid. The cortical thickness is then modelled as the shortest distance between the two delimited boundaries and is available at each vertex of both hemisphere of the brain. More details about the procedure is available in studies 1 (for cortical thickness) and 2 (for subcortical volumes).

3.2 Functional MRI (fMRI): task related and resting state

fMRI follows similar magnetic principles as to structural MRI. However, the origin of the detectable MR signal lies in the fact that the magnetic state of hemoglobin (Hb) depends upon its oxygenation, thus changes in oxygen saturation of the hemoglobin produce a change in the local MR signal. This phenomenon is called the Blood Oxygenation level-dependent (BOLD) signal (Uluda, 2005). More precisely, the deoxyhemoglobin (deoxygenated hemoglobin) is paramagnetic and provides the BOLD signal. When neural activity increases in the brain (i.e. activation), it is translated by an increase in oxygenation of the local blood flow and higher consumption of oxygen.

We could identify two types of functional neuroimaging studies of hallucinations in the literature: state and traits studies (Zmigrod et al., 2016). In state studies, participants are scanned while experiencing a hallucination and indicate its onset and offset with a button press. State studies include within subject designs, involving a contrast of brain activity in the resting versus non-resting state. In trait studies, the comparison is usually between hallucinators and non-hallucinators with regard to their brain activity while they rest or perform experimental tasks.

In this project, the task in place will be the MGT but in an fMRI setting (detailed in study 4), where we will measure the course of activations before, during and after the MGT-induced visual illusion. The second type of fMRI, resting state fMRI, will be used in study 5. It relies on periods of unconstrained brain activity that takes place during rest. Intrinsic and spontaneous brain activity convey information concerning functional brain properties more related to neurobiology than cognitive processes. Resting State-fMRI (rs-fMRI) represents interregional correlation of brain activity measured at rest and organized into coherent networks (Husain &

Schmidt, 2014). Therefore, resting state signals are considered to be related to intrinsic neuronal activity (Fox, 2010), and could inform the topologic organization of neural networks at the baseline.

4. Overview of the studies conducted

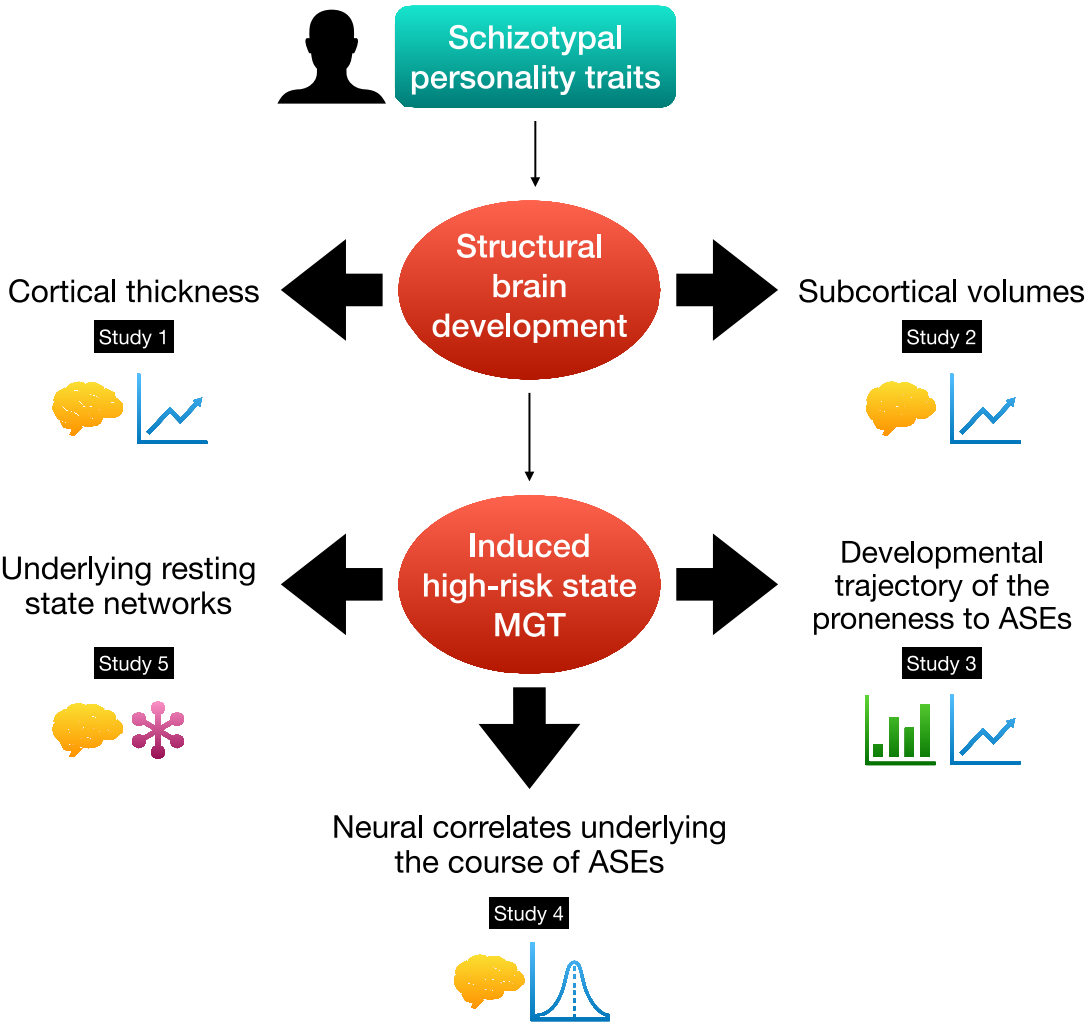


Figure 5: Studies included in the PhD thesis

Study 1: is a neuroimaging structural study that investigates longitudinal developmental trajectories of cortical thickness in relation to schizotypal dimensions along adolescence.

Study 2: is a neuroimaging structural study that investigates longitudinal developmental trajectories of subcortical structures volumes in relation to schizotypal dimensions along adolescence.

Study 3 is a behavioral developmental study of the proneness to ASEs in relation to self-reported schizotypy, including individuals from 7 to 28 year old.

Study 4 is a neuroimaging fMRI study investigating the neural correlates preceding and ongoing ASEs as induced with the MGT.

Study 5 is a neuroimaging rs-fMRI study investigating the resting state networks of adolescents experiencing ASEs as induced by the MGT. The link with self-reported schizotypy is examined in cross-sectional and longitudinal analyses.

Chapter III

Empirical section

1. Study 1 – Developmental trajectories of cortical thickness in relation to schizotypy during adolescence*

Abstract

Investigating potential grey matter differences in adolescents presenting higher levels of schizotypy personality traits could bring further insights into the development of schizophrenia spectrum disorders. Research has yet to examine the morphological correlates of schizotypy features during adolescence prospectively, and no information is available on the developmental trajectories from adolescence to adulthood. We employed mixed model regression analysis to investigate developmental trajectories of cortical thickness (CT) in relation to schizotypy dimensions in a cohort of 109 adolescents from the general population for whom MRI-scans were acquired over a five-year period, culminating in a total of 271 scans. Structural data were processed with FreeSurfer software, statistical analyses were conducted using mixed regression models following a ROI-based approach, and schizotypy was assessed with the Schizotypal Personality Questionnaire (SPQ). Accelerated thinning was observed in the posterior cingulate cortex in relation to high levels of positive schizotypy, whereas high levels of disorganized schizotypy were associated with a similar trajectory pattern in the anterior cingulate cortex. The developmental course of CT in the prefrontal, occipital and

* This is a reprint of Derome, M., Tonini, E., Zöller, D., Schaer, M., Eliez, S., Debbané, M. Developmental trajectories of cortical thickness in relation to schizotypy during adolescence (2020). Manuscript published in *Schizophrenia Bulletin.* 10.1093/schbul/sbaa020.

cingulate cortices differed between adolescents expressing higher versus lower levels of negative schizotypy. Participants reporting high scores on all schizotypy dimensions were associated with differential trajectories of CT in posterior cingulate cortex and occipital cortex. Consistently with prospective developmental studies of clinical risk conversion, the negative schizotypy dimension appears to constitute the most informative dimension for psychosis-related psychopathology, as its cerebral correlates in adolescents most closely overlap with results found in clinical high-risk for psychosis studies.

Introduction

The schizotypy construct encompasses genetic, biochemical, neurocognitive, phenotypic and behavioral characteristics that confer a latent vulnerability to develop psychotic disorders (Fonseca-Pedrero et al., 2014a). It connects with schizophrenia spectrum and other psychotic disorders at the level of factorial analyses in samples expressing non-clinical to clinical symptoms, yielding three factors: a positive factor (delusions and unusual perceptual experiences), a negative factor (social and physical anhedonia), and a disorganization factor (odd speech and behaviors). Individuals who report higher levels on psychometric schizotypy indeed express subtle emotional, behavioral, neurocognitive, psychophysiological and social impairments similar to patients with schizophrenia or schizotypal disorder (Barkus et al., 2005; Debbané et al., 2015; Flückiger et al., 2016). Perhaps most significantly, from a prospective standpoint, longitudinal studies illustrate how schizotypy significantly predicts the risk for conversion to psychosis, in high risk for psychosis samples, familial risk samples, and personality disorder samples, but also in the general population samples (Debbané et al., 2015). As such, when reviewing 6 longitudinal studies including 7282 participants from the general

population, 207 of them converted to psychosis (2.8%) (Debbané et al., 2015). Schizotypy thus constitutes a relevant developmental predictive factor when looking at clinical high-risk (Morrison et al., 2006) of psychosis. Yet to date, little attention has been given to the neural underpinnings of schizotypy during adolescence, which represents a critical period for brain maturation (Tamnes et al., 2017), and a key period for clinical high-risk preceding first onset of psychosis (Thompson et al., 2001).

From such a neurodevelopmental point of view, accumulated evidence in at-risk subjects who go on to develop psychotic disorders suggests atypical brain morphology (Ziermans et al., 2012) and atypical patterns of cerebral maturation (Schneider et al., 2016). A study following clinical high risk (CHR) individuals observed a steeper rate of thinning in medial and lateral prefrontal regions for converters in comparison to non-converters (Cannon et al., 2015b). In another study, young CHR converters exhibited smaller surface area in rostral anterior cingulate, prefrontal regions and parahippocampal gyrus when compared to non-converters and remitters (Chung et al., 2019b). An additional study on CHR found that those who converted to psychosis exhibited less grey matter (GM) volume in the left para hippocampal cortex than those who did not convert (Mechelli et al., 2011b). Following the spectrum, it is also of interest to integrate cross-sectional results obtained in cohorts of patients with first episode psychosis (FEP) (Asmal et al., 2018; Crespo-Facorro et al., 2011): CT alterations are localized in frontal (Asmal et al., 2018) and temporal areas (Dickey et al., 2002; Janssen et al., 2009). When considering patients with schizotypal personality disorders (SPD), a review identified structural brain abnormalities in superior temporal gyrus, para hippocampus, and thalamus (Dickey et al., 2002; Ettinger et al., 2014). Finally, at the clinical endpoint of the continuum, neuroimaging studies report brain structure abnormalities in schizophrenia diagnosed individuals, including grey matter (GM) volume reductions across the cortex, hippocampus and amygdala (Cannon et al., 2015; Chua & McKenna, 1995). Altogether,

these studies point to the progression of morphological brain alterations along the continuum of psychosis. However, little is known concerning the common cerebral endophenotypes between adolescent schizotypy and CHR, siblings as well as clinical samples.

To date, researchers studying schizotypy in the general population have contributed slightly more than a handful of studies of brain morphology in association to total or dimensional scores on schizotypy measures, yielding a set of disparate results (DeRosse et al., 2015; Ettinger et al., 2014; Evans et al., 2016; Modinos et al., 2010; Moorhead et al., 2009; Nenadic et al., 2015; Wiebels et al., 2016; Zou et al., 2015). The studies focusing on adult populations report that adults who score higher either on the SPQ total score (DeRosse et al., 2015) or on each dimension (Wiebels et al., 2016), typically show less GM volume and CT in the frontal and temporal lobes, as well as anterior cingulum and insula (Moorhead et al., 2009; Zou et al., 2015). In contrast, two studies report that high scorers on positive schizotypy present greater GM volumes in posterior cingulate cortex and precuneus (Modinos et al., 2010). Only two cross-sectional studies examined schizotypy during adolescence. The first study (Wang et al., 2015) included typically developing youths with high schizotypy (n=35) from 16 to 23 years old, who were found to display lower GM density around the region of the insula and dorsolateral Prefrontal gyrus. In the second study (Evans et al., 2016) involving youths (n=28) from 6 to 17 years of age, the positive schizotypy dimension was negatively associated with GM density in temporal and caudate volumes. While interesting, these studies were potentially underpowered, and none of them made use of longitudinal, multiple time points for each subject.

The current prospective study provides the first examination of the developmental trajectories between psychopathological traits of schizotypy during adolescence and cerebral endophenotypes in a longitudinal fashion. We propose a longitudinal mixed regression models

approach, including data from 109 adolescents with one to five time points of visits. They will first be clustered into high and low scorers on each individual schizotypy dimension. Secondly, they will be defined by their schizotypy profiles, representing the combined levels of the three dimensions. The present study carries the potential to inform whether alterations in cerebral morphology found in CHR and/or siblings samples can also be observed in relation to schizotypy during adolescence.

We hypothesize that CT maturation patterns of individuals expressing high schizotypal features would relate to those found in community youths expressing high schizotypy (prefrontal cortex (PFC), temporal and caudate regions)). We anticipate that part of these patterns may reflect underlying pathogenesis, as seen in the initial stages of risk for psychosis. Therefore, we expect developmental differences in brain regions sharing commonalities with CHR converters (such as lateral and medial prefrontal, rostral anterior cingulate and/or para hippocampal regions), which would convey the common basis of risk for psychosis between adolescent schizotypy and CHR converters. The value of such research question is to find the earliest cerebral signatures of psychotic pathogenesis.

Methods

Participants

The study included a sample of 109 typically developing (TD) participants (60 males, 49 females). TD were recruited in the community and screened for the absence of acute psychotic phase, and estimated intellectual functioning on the Block Design and Vocabulary subtests below 1 std.dev of the developmental norm (based on the Cubes and vocabulary subtests of the Weschler Scales of Intelligence for children (WISC-IV) or for participants older than 18 y.o,

the Wechsler Adult Intelligence Scale (WAIS-IV) detailed in the *supplementary material-Appendix 3*). From the original sample of 123, 14 adolescents were excluded; 2 of them because they did not have a measure of vocabulary subtest, 7 because they suffered from diagnosed anxiety disorders and depression, 4 because they were diagnosed with Attention-Deficit/Hyperactivity Disorder (ADHD) and 1 presented schizoaffective disorder (see *supplementary material Appendix 3* for more details). All participants were French-native speakers, community adolescents and young adults with normal or corrected to normal vision. Recruitment was done by word of mouth and through advertisement in youth community centers around the Canton of Geneva. At the first visit the mean age was 15,98 (SD = 1,83), ranging from 12 to 20 years old (y.o). Individuals were enrolled in this longitudinal study and were assessed at multiple time points within a five years interval. Number of assessments varied between participants: a total of 271 scans was acquired comprising 27 individuals with one scan, 26 with two, 32 with three and 24 with four scans (see Figure 6 and Table 3). Participants received a financial compensation, and written consent was obtained from themselves or their parents (if they were under 18), under protocols approved by the local ethical commission (Commission Centrale d'éthique de la Recherche des Hôpitaux Universitaires de Genève).

Psychological Measures

We assessed adaptive behaviors using Adult Self Report and Youth Self Report as a control measure for internalizing and externalizing. Schizotypal personality traits were evaluated with the SPQ, which define 3 dimensions (positive, negative and disorganized. Refer to *supplementary material Appendix 3* for details on these measures.

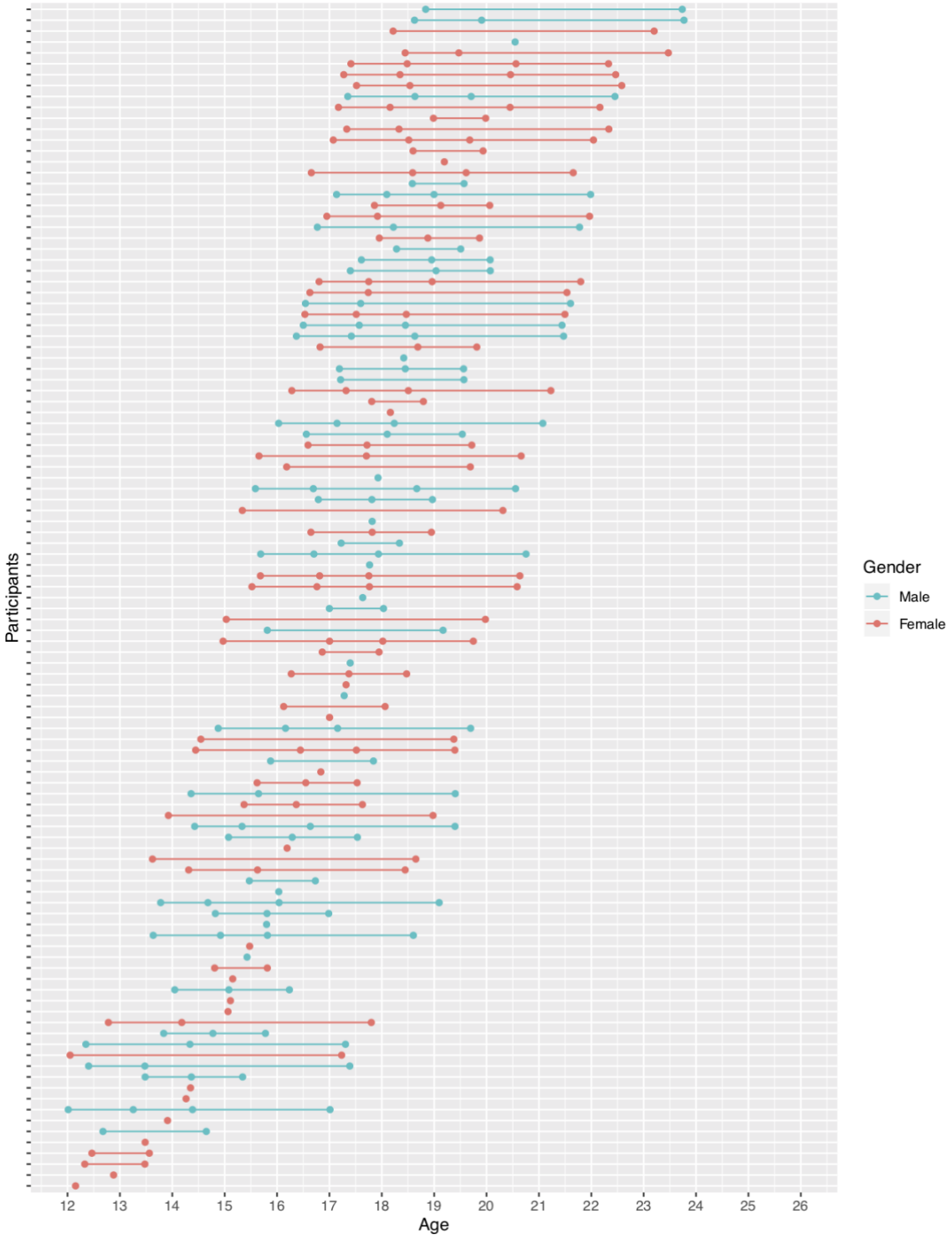


Figure 6: Age distribution of participants

blue represents males, pink represents females

Partition of Participants in Groups: Single dimensions analyses

To assess the potential influence of each single dimension of schizotypy on CT development we created groups of participant based on their SPQ score at first time point for each dimension (i.e., positive, negative, and disorganized) separately using optimal k-means clustering for univariate data implemented in R (*see supplementary material Appendix 3 for more details*). The division yielded two subgroups for each dimension: high positive scorers (HPS) and low positive scorers (LPS); high negative scorers (HNS) and low negative scorers (LNS); high disorganized scorers (HDS) and low disorganized scorers (LDS).

Partition of Participants in Groups: Overall combined score analyses

For the subsequent analysis, we further analyzed the combined scores on the three SPQ dimensions. Using a double procedure combining K-means and Hierarchical agglomerative (Ward's method) clustering in R, partitioning of participants resulted into three clusters based on their SPQ scores in all dimensions at first time point to reflect their profiles on the three dimensions taken together. Among the three resulting clusters, one represented participant scoring high in all three dimensions classified as high schizotypy profiles (HS). The second cluster retained participants scoring intermediate in all three dimensions, referred to as intermediate schizotypy profiles (IS). The third cluster included participants scoring low in all three dimensions, the low schizotypy profiles (LS) (*see supplementary material Appendix 3 for cluster analysis details*).

MRI Acquisition and Pre-processing

Acquisition and preprocessing methods were identical to both analyses.

Acquisition.

T1-weighted neuroimaging data was acquired using a 3-Tesla Siemens Trio 3T scanner at the Hôpitaux Universitaire Genevois (HUG), or at the Brain Behavioral Laboratory at University of Geneva (BBL). A 3D volumetric pulse sequence was used, with the following parameters: TR = 2500 ms, TE = 3 ms, flip angle = 8°, acquisition matrix = 256 x 256, field of view = 22 cm, slice thickness = 1.1 mm, 192 slices.

MRI Pre-processing.

To obtain an accurate three-dimensional cortical model, images were processed using *FreeSurfer* software version 5.3 (http://surfer.nmr.mgh.harvard.edu). Processing steps were conducted following the *Freesurfer* pipeline for fully automated preparation of images, included resampling of the surface into cubic voxels, skull stripping, intensity normalization, white matter segmentation, surface atlas registration, surface extraction and gyrus labeling. After preprocessing, each participant was registered to the spherical atlas *fsaverage* in *FreeSurfer*. For each individual, resulting white matter and pial surfaces were visually checked and manually corrected when necessary. CT was measured as the shortest distance between the two surfaces and was computed at each vertex of both hemispheres. CT was smoothed using a full width at half maximum kernel of 10mm and the cortex was subdivided into 66 parcels based on the Desikan-Kiliani cortical atlas provided in FreeSurfer. The parcellation of the brain translates in a ROI-based approach; we extracted 66 values of CT per participants (one per regions) covering the whole brain cortical areas.

To extract reliable thickness estimates, images were automatically processed with the longitudinal stream*(Reuter & Fischl, 2011)* in FreeSurfer. Specifically an unbiased within-

subject template space and image*(Reuter et al., 2012)* is created using robust, inverse consistent registration*(Reuter et al., 2010)*. Several processing steps, such as skull stripping, Talairach transforms, atlas registration as well as spherical surface maps and parcellations are then initialized with common information from the within-subject template, significantly increasing reliability and statistical power. Although manual edits from the previous steps were incorporated in the longitudinal scans, each resulting scan was visually checked again, and manually corrected if needed. Note that individuals with a single time point were also processed through the longitudinal stream to ensure consistency of processing.

Statistical analysis: Descriptive statistics

First, we performed descriptive cross-sectional statistical analyses comparing the participants' subgroups obtained from clustering in order to investigate whether they differed on their demographic characteristics. Mann-Whitney U tests were conducted in SPSS Version 24.0 on demographic and cognitive variables including age, ASR/YSR internalized and externalized behaviors score, and Wechsler's WISC/WAIS-IV Block Design and Vocabulary standardized score. We additionally combined WISC/WAIS two subtests into a measure of intellectual functioning using the average of the subtests.

Statistical MRI analyses: Developmental Trajectories

We performed mixed model regression analyses (Dedrick et al., 2009; Mancini et al., 2019; Mutlu et al., 2013) using in-house script to compare trajectories of CT between high and low level of each schizotypy dimension. Mixed modeling has proven to be a reliable method (Dedrick et al., 2009) for the statistical analysis of nested data, such as our dataset comprising

multiple time points. Age and schizotypy groups were modeled as a fixed effect and within-subject factors as random effects using the nlmefit function in MATLAB R2016b (script available at https://github.com/danizoeller/myMixedModelsTrajectories). For each of the 8 analysis: sex, location of MRI scanner, ASR/YSR internalized and externalized behaviors scores, and an average score between Wechsler's WISC/WAIS-IV Block Design and vocabulary standardized scores were entered as mean-centered (demeaned) covariates of no interest.

Developmental trajectories were estimated by fitting random-slope models (Mancini et al., 2019a) to our data (constant, linear, quadratic or cubic, each corresponding to a different relationship between age and CT) while taking into account both within and between-subject effects. Then, the most suitable model order was selected based on the Bayesian Information Criterion (Heng Peng & Lu, 2012). For the individual dimensions, the grouping variable consisted of a vector with two levels (coded as 0: low SPQ scores and 1: high SPQ scores), for the three dimensions analysis, the grouping vector was coded with three levels (1: low, 2: intermediate, 3: high scorers). Finally, the significance of between group differences in the intercept and slope were evaluated using a log-likelihood ratio test. Thus, we obtained a comparison between the intercept (group effect) and the slope of developmental trajectories (group x age interaction effect) of the CT of each group. All retained results survived a threshold of $p<0.05$, corrected for multiple comparisons using False Discovery Rate (FDR). For more details, see *supplementary material Appendix 3*.

Results

1. Descriptive measures

Variable	LPS	HPS		LNS	HNS		LDS	HDS										
N (Total = 109)	78	31		68	41		68	41										
Gender (%)	28 F (35.8)	21 F (67.7)		28 F (41.2)	21 F (51.2)		25 F (36.7)	24 F (58.5)										
Nbr of scans	195	76		171	100		162	109										
	Mean	**SD**	**Mean**	**SD**	**Sig.**	**g Hedges**	**Mean**	**SD**	**Mean**	**SD**	**Sig.**	**g Hedges**	**Mean**	**SD**	**Mean**	**SD**	**Sig.**	**g Hedges**
Age	16,03	1,82	15,92	1,9	n.s		16,04	1,86	15,82	1,82	n.s.		16,03	1,86	15,95	1,8	n.s	
SPQ positive	5,28	3,09	17,52	5,03	***	3,27	6,71	5,27	12,02	7,51	***	0.85	6	4,7	13,34	6,98	***	1,3
SPQ negative	5,19	4,05	8,55	4,47	***	0,8	3,23	2,18	11,04	2,56	***	3.35	4,08	3,99	7,98	4,54	**	0,93
SPQ disorganized	4,76	3,23	8,84	3,14	***	1,27	4,84	3,44	7,44	3,48	***	0,75	3,54	2,10	9,85	1.9	***	3.11
ASR/YSR Internalizing	50,28	9,8	59,48	9,05	***	0.9	46,86	8,40	59,28	8,45	***	1.48	49,96	9,68	57,78	9,94	***	0,8
ASR/YSR Externalizing	55,14	9,58	59,48	8,7	*	0.46	54,86	10,28	57,98	8,4	n.s		54,18	9,57	60,02	8,28	**	0,64
WISC/ WAIS (Block Design)	11,2	2,94	9,23	3,05	***	0,66	11,02	2,87	10,26	3,29	***	0.25	10,85	3,2	10,32	2,92	n.s	
WISC/ WAIS (Vocabulary)	11,46	11,1	11,39	6,11	n.s		11,25	3,08	11,64	3,14	n.s		10,91	3,29	12,32	2,57	*	0.46
IQ (average BlockDe and Voc)	11,34	2,6	10,31	2,37	*	0.4	11,13	2,58	10,95	2,62	n.s		10,88	2,74	11,32	2,33	n.s	

Table 3: Descriptive statistics of groups based on positive, negative and disorganized dimension

LPS stands for low positive scorers; HPS, high positive scorers; LNS, low negative scorers; HNS, high negative scorers; LDS, low disorganized scorers; HDS, high disorganized scorers; F, female; SD, standard deviation; ASR, Adult Self Report; YSR, Youth Self Report; WISC, Wechsler Intelligence Scale for Children; WAIS, Wechsler Adult Intelligence Scale. All variable values are measures from first time point. Mean difference between the groups is significant at (*) p <0.05. ; (**) p <0.01 ; (***) p <0.001 ; n.s. stands for not significant. Hedges g were calculated as measures of effect sizes

1.1 Dimensional analysis

Descriptive statistics for the groups based on high and low scorers in each dimension of schizotypy at first time point are presented in Table 3. For each analysis, all schizotypy dimensions and internalized behaviors differed significantly between high and low scorers. Whereas age and gender were balanced between groups.

1.2 Profile analyses

Descriptive statistics of the three groups created on SPQ scores on all schizotypy dimensions at first time points and representing schizotypy profiles are presented in Table 4.

Variable	LS		IS		HS	
N (Total = 109)	51		42		16	
Gender (%)	18 F (35.3)		21 F (50.0)		10 F (62.5)	
Number of scans	126		100		45	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
Age	16.13	1.79	15.93	1.86	15.65	1.94
SPQ Positive***	3.86	2.60	10.12	3.29	21.00	4.68
SPQ Negative***	3.06	2.46	8.17	3.57	11.06	4.04
SPQ Disorganized***	3.61	2.78	7.00	2.87	10.31	2.55
ASR/YSR Internalizing***	46.59	8.56	56.79	7.92	62.81	9.40
ASR/YSR Externalizing***	52.84	9.71	58.81	8.03	60.56	8.73
WISC/WAIS (Block Design)	11.27	2.72	10.33	3.13	9.50	3.79
WISC/WAIS (Vocabulary)	11.02	3.33	11.93	2.97	11.50	2.66
IQ (average BlockDE and Voc)	11.147	2.51	11.13	2.64	10.50	2.81

Table 4: Descriptive statistics of groups based on the profiles

*LS stands for low schizotypy profile; IS, intermediate schizotypy profile; HS, high schizotypy profile; F, female; SD, standard deviation; ASR, Adult Self Report; YSR, Youth Self Report; WISC, Wechsler Intelligence Scale for Children; WAIS, Wechsler Adult Intelligence Scale.*** The mean difference between the groups is significant at p <0.001.*

2. Structural MRI analyses: Developmental Trajectories

2.1 Dimensional analyses

When applying mixed model regression analyses for positive, negative and disorganized schizotypy separately, we found significant between groups differences in CT developmental trajectories for each dimension. Significant results are presented below; please refer to the *supplementary material Appendix 3* for results including all 66 regions.

Positive schizotypy dimension

For both groups, CT developmental trajectories of the left posterior cingulate cortex were linearly decreasing and displayed significant differences of slope in relation to positive schizotypal dimension (p=0.016, FDR-corrected for multiple comparisons), with HPS exhibiting quicker CT thinning compared to LPS over the entire age-range (*see Figure 7A*).

Disorganized schizotypy dimension

Among the 66 cortical regions studied, the caudal anterior cingulate showed a slower linear cortical thinning with age in adolescents with high disorganization scores compared to those with low disorganization scores (p=0.009, FDR-corrected, *see Figure 7B*).

Negative schizotypy dimension

In the left hemisphere, quadratic trajectories of CT in the pars triangularis, the rostral middle frontal and lateral orbitofrontal cortices showed significantly different slopes of the trajectories between HNS and LNS (respectively: p=0.045, p=0.004, p<0.000, all FDR-corrected). In HNS, CT in these three frontal regions showed a peak of thickness around 17

y.o, while CT of LNS followed a U-shaped-like decrease until its lowest measure around 20 y.o (*see Figure 7E, 7C, 7G*). In all regions, the maturation of CT is delayed in HNS, and followed by an accelerated cortical thinning.

In the right lateral occipital cortex, HNS displayed a peak of CT around 18 y.o, while the CT of LNS was at its highest at an early age and then gradually decreased until early adulthood, indicating a significant difference in quadratic trajectory slopes throughout adolescence (p<0.000, FDR-corrected, *see Figure 7D*).

Concerning the right isthmus cingulate region, LNS showed a gradual U-shaped-like thinning of CT, whereas HNS exhibited linear excessive cortical thinning compared to LNS over the entire age-range (p=0.011, *see Figure 7F).*

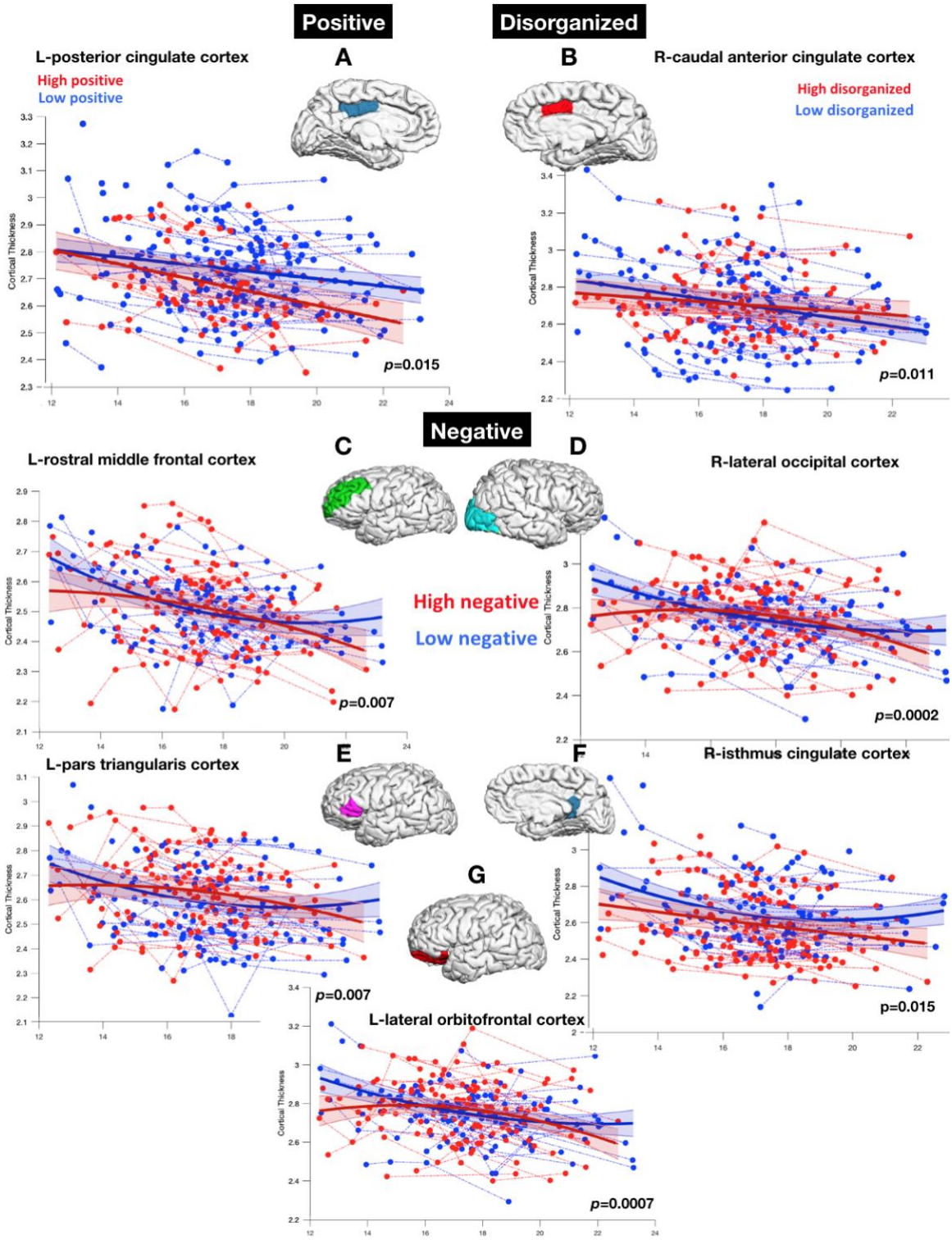


Figure 7: Individual schizotypy dimensions.

*Developmental trajectories of **A** left posterior cingulate cortex in relation to positive schizotypy dimension, **B** right caudal cingulate cortex in relation to disorganized schizotypy dimension, **C** left rostral middle frontal cortex, **D** right lateral occipital cortex, **E** left pars triangularis*

*cortex, **F** right isthmus cingulate cortex, and **G** left lateral orbitofrontal cortex in relation to negative schizotypy dimension. p-values represent significant interaction (Group x Age) effect.*

2.2. Combined scores analyses

When examining the combined scores of the three schizotypy dimensions, HS, IS and LS displayed significant differences in the development of two cortical brain regions. In the R-isthmus cingulate cortex, CT trajectories were significantly different across all three subgroups *(p*=0.005, FDR-corrected) as well as in the R-lateral occipital cortex (p=0.005, FDR-corrected). In both cases, it seems when observing the figure, that CT followed quadratic U-shaped trajectory for the LS profile, an inverted U-shaped trajectory for HS and a linear trajectory for the intermediate group (*see Figure 8*). In the right isthmus cingulate cortex, LS displayed the highest CT in early adolescence, which gradually decreased over the covered age interval. HS exhibited the lowest CT in early adolescence in this region, with gradual thinning until early adulthood. Finally, IS adopted an "intermediate" linear developmental trajectory, positioned in between CT measures of HS and LS. In the right lateral occipital cortex, LS showed decreasing CT from age 12, while CT of HS remained at constant value until 17 y.o where a subsequent slow decrease occurs until adulthood. Interestingly, IS again exhibited an "intermediate" linear CT developmental trajectory, relatively to HS and LS.

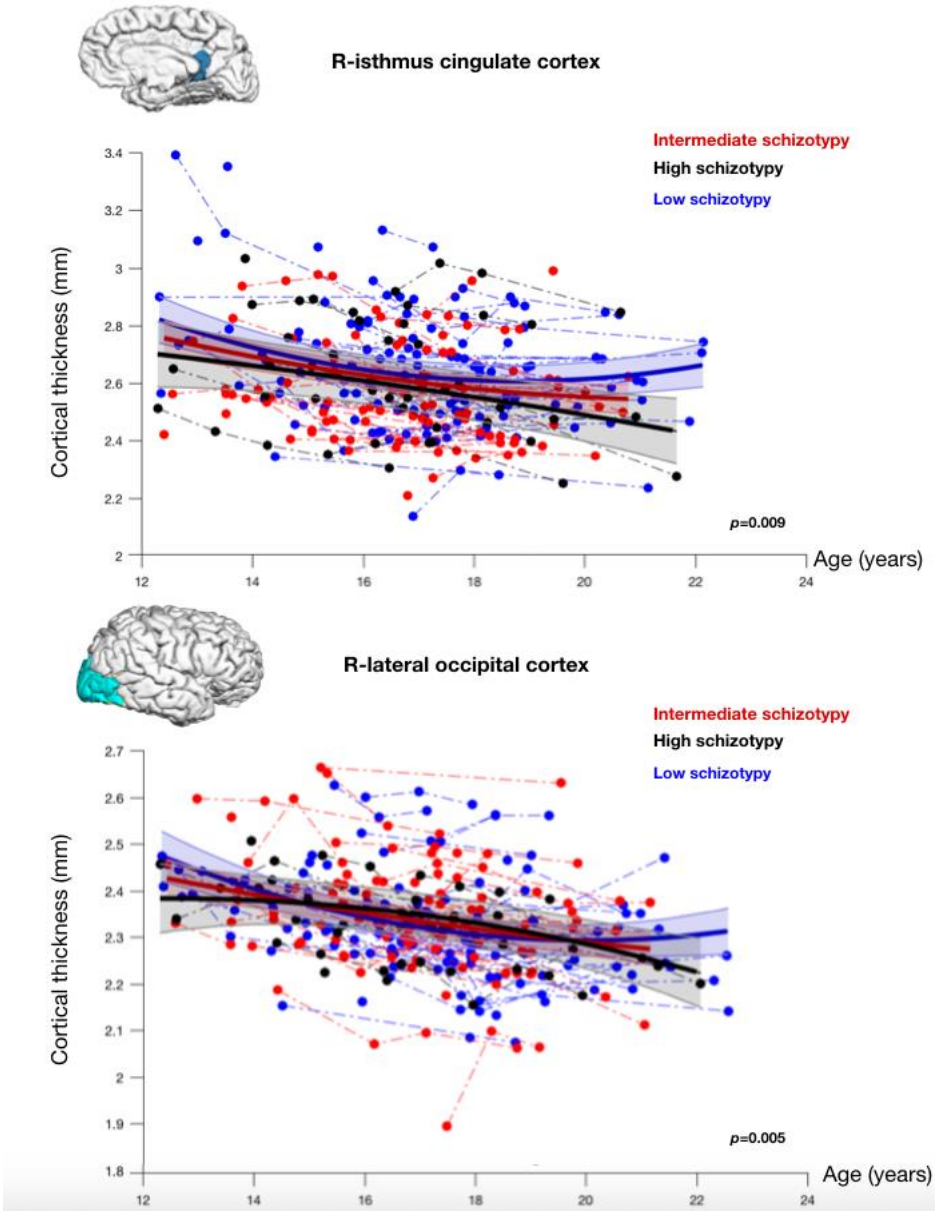


Figure 8: Schizotypy profiles.

*Developmental trajectories of **TOP** right isthmus cingulate cortex and **BOTTOM** right lateral occipital cortex in relation to schizotypy profiles (high, intermediate, and low). p-values represent significant interaction (Group x Age) effect.*

Discussion

This longitudinal study examined cortical thickness (CT) developmental trajectories in relation to the dimensions of schizotypy in a group of non-clinical adolescents. When examining the potential associations of each single dimension of schizotypy individually, we first observed that adolescents reporting a higher level of positive schizotypy showed an accelerated thinning within the left posterior cingulate cortex (PCC) CT. Furthermore, those adolescents reporting a higher level of disorganized schizotypy showed distinct pattern of CT development around the caudal anterior cingulate region when compared to lower disorganized schizotypy expression. In relation to the negative dimension of schizotypy, the development of CT in the prefrontal, occipital and cingulate cortices appeared to differ between adolescents expressing higher and those expressing lower levels of negative schizotypy. In our subsequent analyses, when examining subgroups clustered as high, intermediate, and low on all schizotypy dimensional scores, we observed distinct patterns of CT development involving two of the same regions as when investigating the negative dimension: PCC and lateral occipital cortices. This longitudinal study on schizotypy allows us to disentangle the extent to which structural brain abnormalities form part of a general vulnerability to the disorder or are only present in individuals who subsequently develop schizophrenia, thus characterized as markers associated with clinical risk. In the following discussion, we will assess, on one-hand, results involving the same brain regions as those involved in the neuroimaging studies examining clinical high-risk CT trajectories of subjects who convert to psychosis. On the other hand, we will identify brain regions atypical CT developmental curves simply linked to inter-individual variability on the schizotypy trait. We will address this duality by comparing our results with existing longitudinal studies involving CHR converters and individuals at familial high-risk, as well as general population studies on schizotypy.

[High vs Low Positive dimension]

Adolescents expressing higher levels of *positive* schizotypy displayed a significantly more pronounced thinning of the PCC when compared to lower positive scorers. Similar abnormal thinning over time was found in the cingulate of individuals at familial high risk (Bois et al., 2015), suggesting that atypical CT development in this region may be a common genetic marker of general vulnerability to psychosis. As some authors have suggested, a related cognitive endophenotype may relate to a failure to distinguish clearly between internal and external events, which in patients with schizophrenia links to reduced PCC volume (Hulshoff Pol et al., 2001).

[High vs Low disorganized dimension]

A slower linear cortical thinning trajectory was observed for the adolescents scoring high on disorganization schizotypy, in the right caudal anterior cingulate cortex CT, when compared with lower disorganized schizotypy scorers. Although the slope of the developmental trajectory was steeper in LDS, HDS displayed lower CT values until 18 years of age. In comparison, it has been found that the anterior cingulate cortex is thinner in familial high risk (Bois et al., 2015), as well as in patients with SPD (Hazlett et al., 2008), FEP (Narr et al., 2005) and schizophrenia (Kuperberg et al., 2003). It is thus tempting to interpret that the pattern found in HDS non clinical adolescents represents a form of compensation mechanism protecting them from the significant loss of GM seen in clinical populations, although future studies should examine more closely the mechanisms that would underlie this putative protective mechanism, which leads HDS and LDS to present equivalent CT after 18 years of age.

[High vs Low Negative dimension]

HNS showed a delay in right *lateral occipital* CT maturation when compared to LNS, with thinning only starting at around 18 y.o. Recent literature concerning the impact of psychotic symptoms on morphology of lateral occipital lobe reports CT reduction in unaffected relatives of schizophrenia patients (Bois et al., 2015b; Yang et al., 2010), in first-episode schizophrenia patients (Sprooten et al., 2013), and schizophrenia patients (Kong et al., 2015; Rimol et al., 2010). The trajectory displayed within the *isthmus cingulate* cortex, with an excessive cortical thinning in adolescents expressing higher negative traits. The isthmus representing the posterior part of the cingulate, and as mentioned above, the observed atypical trajectory of CT is retrieved in unaffected familial high risk (Bois et al., 2015b) and seems to be related to the symptomatology of schizophrenia such as failure in differentiation between internal and external thoughts explained earlier (Sowell et al., 2000). This may influence the cognitive endophenotype associated with schizotypy, but not necessarily contribute to the emergence of psychotic disorders.

Expressing high *negative* schizotypy was also associated with delayed maturation and later decrease of CT in three *prefrontal* regions (pars triangularis, orbitofrontal and middle frontal cortices). LNS displayed a slightly U-shaped decrease of CT in each prefrontal region, concordant with studies investigating CT development in typical adolescence (Vijayakumar Nandita et al., 2016), while HNS exhibited an inverted U-shaped increase trajectory. Cannon and colleagues (Cannon et al., 2015) showed that CHR converters exhibited steeper rate of GM loss in superior and middle frontal and medial orbitofrontal regions when compared to non-converters and HC. Our results further relate to findings of Chung and colleagues, who showed that CHR converters at follow up exhibited smaller surface area in lateral and medial prefrontal regions (Chung et al., 2019). In conjunction with clinical evidence suggesting that negative schizotypy (mostly anhedonia) rather than positive schizotypy might be more predictive of conversion to CHR states (Flückiger et al., 2016), these prefrontal alterations may speak

directly to emerging risk states and conversion to clinical forms of psychosis.

[Schizotypy profiles]

Consistently with some studies using the SPQ total score, our analysis with this sum score yielded differential CT development of the right *isthmus cingulate* cortex and right *lateral occipital* cortex in HS, IS and LS. In HS, maturation of CT in these regions appeared delayed, and followed by significantly more pronounced thinning. Interestingly, IS display intermediate CT developmental trajectories in these two regions, in between that of HS and LS. We could hypothesize that this last result illustrates the continuum of psychosis theory (Tijms et al., 2015), with significant focal relationships between cerebral maturation and degree of expression of schizotypy. Several studies have reported reduced CT in schizophrenia, with intermediate measures of CT in frontal and cingulate cortex in relatives (Oertel-Knöchel et al., 2013) or in SPD patients (Watsky et al., 2016), compared to healthy controls. In addition, in a study comparing psychotic patients, non-clinical auditory hallucinations and healthy controls, it was shown that CT in temporal lobe is intermediate in the non-clinical hallucinating group, lowest in patients and highest in controls (van Lutterveld et al., 2014). Thus, in the present sample of adolescents, we could argue that a similar process is already active at the non-clinical stage in two key regions known to be involved in internally directed thoughts and visual processing. Similarly, individuals expressing higher schizotypal personality traits present the most atypical CT trajectory when compared to low schizotypy profiles. Moreover, although the association of schizophrenia's visual hallucinations and the occipital lobe is known, whether the whole occipital lobe is involved or just some parts or whether it is damaged before other regions remains open to investigation (see review, (Hazlett et al., 2008). Here, we can only infer on the differential trajectory in the three schizotypy profiles and hypothesize that CT in these regions follows a similarly gradual atypical CT development which could relate to

specificities in information processing, but this remains to be thoroughly researched. Strikingly, the two regions identified in the present profile analysis correspond to two of the regions showing atypical developmental trajectories in adolescents expressing higher negative schizotypy. This last observation seems to corroborate the hypothesized psychosis-predictive role conveyed by the negative dimension in those regions.

[Limitations]

There are a number of limitations to this study that should be taken into account. We investigated developmental trajectories only during the second decade of life and throughout adolescence; therefore, similar attention could be given to major changes appearing during childhood. Secondly, the main analyses were conducted with FreeSurfer, parcellating the brain using an atlas from the software, which is consistent with most of previous literature and allows the use of indices of fit for model selection. However, for larger parcellated structures, it is important to bear in mind that developmental patterns might be different within regions. Another limitation is the use of a self-rated instrument; future studies should include an observer rater (interviews). While longitudinal schizotypal traits studied in the general population is still a burgeoning field, further research using larger cohorts is required. Importantly, cohorts of adolescent siblings of patients with schizophrenia would help evaluate the strength and value of the results found in our general population sample We contend that enhanced longitudinal characterization (with more time points or following the converters to psychosis) will provide fruitful grounds for uncovering the developmental processes preceding high-risk states that signal pathogenic markers, and may eventually inform prevention strategies.

[Conclusion]

This longitudinal study allowed us to draw new hypothesis concerning the common cerebral endophenotypes between adolescent schizotypy and CHR, siblings, and well as clinical samples. However, given the lack of direct comparison between these populations, future research is required to validate the potential risk-predictive value of negative schizotypy in clinical population and to understand the mechanisms driving the differences as well as their functional and behavioral implications.

2. Study 2 – Developmental trajectories of subcortical structures in relation to dimensional schizotypy along adolescence[**]

Abstract

Morphological abnormalities of subcortical structures have been consistently reported along the schizophrenia clinical spectrum, and they may play an important role in the pathophysiology of psychosis. However, the question arises whether these subcortical features are consequences of medication and illness chronicity, or if they contribute to the vulnerability to develop schizophrenia spectrum disorders. If some of the subcortical abnormalities could be evidenced in community adolescents expressing higher schizotypal traits (*psychometric schizotypy*), they could potentially shed light on vulnerability markers. To date, very few studies have examined the link between psychometric schizotypy and volumes of subcortical regions, and none of them have used a longitudinal design. This study sets out to investigate developmental trajectories of subcortical volumes in 110 community adolescents (12 to 20 years old), for whom MRI-scans were acquired over a period of 5 years, reaching a total of 297 scans. Analyses were conducted using Freesurfer, and schizotypal traits were measured with the Schizotypal Personality Questionnaire (SPQ). Using mixed model regression analyses following a region-of-interest approach, we observed differential linear developmental trajectories in four subcortical structures when comparing higher versus lower scorers on the disorganized schizotypy dimension (bilateral hippocampus, left-lateral ventricle and left-

[**]This is a reprint of Derome, M., Zöller, D., Modinos, G., Schaer, M., Eliez, S., Debbané, M. Developmental trajectories of subcortical structures in relation to dimensional schizotypy expression along adolescence (2020). Manuscript published in *Schizophrenia Research.* 10.1016/j.schres.2020.020005

pallidum) and the negative schizotypy dimension (bilateral pallidum, and right-thalamus). All results survived a threshold of $p<.05$ (FDR-corrected) while covarying for the effect of other psychological problems (externalized and internalized psychopathology). These results indicate that expression of higher levels of negative and disorganized schizotypy during adolescence was associated with neural markers linking schizotypy personality features to schizophrenia spectrum disorders.

Introduction

A large number of reviews and meta-analyses of magnetic resonance imaging (MRI) studies have provided empirical quantification on subcortical volume alterations in patients with schizophrenia (Olabi et al., 2011, Haijma et al., 2013b). The most frequently replicated findings are smaller bilateral hippocampi, amygdala, thalamus, nucleus accumbens (NA) and intracranial volumes (ICV), and larger lateral ventricle and pallidum volumes in patients with schizophrenia. Importantly, studies in first episode psychosis patients (FEP) have also identified hippocampus (Adriano et al., 2011), right caudate (Ellison-Wright et al., 2008b) and thalamic (Gilbert et al., 2001) volumetric reductions compared to healthy controls. Furthermore, in clinical high-risk (CHR) for psychosis individuals, reductions in hippocampal (Fusar-Poli et al., 2012) and thalamic (Harrisberger et al., 2016) volumes have also been described, thus suggesting that such abnormalities may be apparent before the onset of frank psychosis. In addition, further evidence that subcortical volume abnormalities are related to schizophrenia and risk thereof come from studies in patients with schizotypal personality disorders (SPD), with converging volumetric abnormalities in the hippocampus, lateral ventricle and thalamus being reported (Buchsbaum et al., 1997; Cannon, 1994; Raine et al., 1992; Fervaha & Remington, 2013). However, other studies found no differences in the

thalamus volume of SPD patients when compared to schizophrenic patients or controls (Byne et al., 2001). For a review of SPD and structural neuroimaging studies, see (Dickey et al., 2002).

Taken together, these results imply that subcortical volume alterations are already observable at the earliest stages of the clinical manifestations of schizophrenia spectrum and other psychotic disorders. Nevertheless, factors such as severity of symptoms, psychological impact of hospitalizations, and antipsychotic treatment potentially contributes to the morphological modifications of the brain observed along the development of spectrum disorders (Jørgensen et al., 2016; Moncrieff & Leo, 2010; Navari & Dazzan, 2009). Thus, studying schizotypy, a personality trait conferring a liability to develop psychosis, provides a unique framework to observe neurobiological mechanisms involved in psychosis phenotypes while avoiding confounding effects of collateral factors such as medication and disease progression. When investigating adolescents from the general population experiencing subclinical psychotic (delusional and hallucinatory) experiences (SPEs), Okada and colleagues (Okada et al., 2018) found significant volumetric enlargements in the left hippocampus, right caudate and right lateral ventricle, as well as a marginally significant enlargement in the left pallidum. The authors hypothesized that subtle volumetric alterations in the left pallidum of adolescents with SPEs who have not reached a diagnostic level might represent a predisposing factor for developing psychosis. They also suggested that the enlargement of hippocampus volume might reflect changes as compensation to prevent conversion to higher-risk states. In another study investigating subcortical structures in relation to psychometric schizotypy, Kühn (Kühn et al., 2012) and colleagues showed a correlation between high schizotypy total score and reductions in thalamic volume. These studies suggest that detailed examination of the associations between the expression of schizotypal personality features during adolescence and morphological brain development may reveal relevant information to understand schizophrenia spectrum and other psychotic disorders.

In terms of typical neurodevelopment, subcortical structures dynamically develop throughout childhood and adolescence and sustain functional roles including attention, memory, executive functioning and emotional processing (Hill et al., 2017). A recent study examining the normative development of subcortical structures (Wierenga et al., 2014) (n=147, from 7 to 23 years old) suggests that the volumes of the caudate, putamen and nucleus accumbens (N.Acc) decrease with age, that the hippocampus, amygdala and pallidum showed an inverted U-shaped trajectory, and that the thalamus exhibited an initial slight increase followed by a reduction in volume. These results provide a framework for the typical developmental trajectory of the aforementioned structures and allow for a comparison with adolescents who express higher level of schizotypy.

To date, studies investigating psychometric schizotypy have employed cross-sectional designs with success in identifying cerebral alterations linked to the expression of schizotypy (Kühn et al., 2012; Okada et al., 2018), but their ability to provide information about developmental trajectories is limited. The present study investigates dynamic changes in subcortical structure development in relation to the three dimensions of schizotypy (positive, negative and disorganized). Specifically, we explored volumetric changes of caudate nucleus, putamen, pallidum, nucleus accumbens, thalamus, amygdala, hippocampus and lateral ventricle using longitudinal mixed regression, in 110 adolescents with one up to 5 visits. These structures are of particular interest, as they have been implicated in schizophrenia (Ballmaier et al., 2008; Mamah et al., 2008). The present prospective study examines developmental trajectories of subcortical volumes in adolescents with higher and lower levels of schizotypy traits during adolescence and will potentially reveal both a common endophenotype with CHR for psychosis states as well as potential protective factors in non-clinical samples. Our primary hypothesis is that the developmental patterns of subcortical volumes of individuals expressing higher schizotypal features would follow that of community individuals expressing high schizotypy.

Moreover, we expect that when common to developmental differences found in CHR-converters, subcortical regions alterations might convey a risk for psychosis. The value of such research question is to find the earliest cerebral signature of psychotic pathogenesis, an endeavor which might be very significant to psychopathology.

Materials and methods

Participants

The present study included a total of 297 MRI-scans from 110 typically developing (TD) adolescents (57 males) recruited as part of an ongoing longitudinal study. Adolescents were aged between 12 and 20 y.o at the first time of visit (mean(age)=16.0, sd= 1.5, n=110). From the 110 adolescents of the first time visit, 77 of them came back for a second visit (Mage=17.3, sd=1.8), 64 for visit 3 (Mage=18.5, sd=2.1) and 46 for visit 4 (Mage=21.1, sd=1.9, n=46), *see Figure 9.* In total, 26 participants were scanned once, 19 twice, 27 three times, 38 four times (see *supplementary Figure* 1 and *appendix 3* for the mean intervals between each scanning session). They were French-native speakers, community adolescents with normal or corrected to normal vision, recruited through word of mouth and advertisement in youth centres around the Canton of Geneva. They were screened for the absence of acute psychotic phase and estimated general intellectual functioning scoring below 1 standard deviation of the developmental norm (based on the Cubes and Vocabulary subtests of the Weschler Scales of Intelligence for children (WISC-IV)(Wechsler D. Wechsler, 2003) or for participants older than 18 y.o, the Wechsler Adult Intelligence Scale(Wechsler D., 1997) (WAIS-IV). Participants received a financial compensation for their time, and written consent was obtained from themselves or their parents (if they were under 18), under protocols approved by the local ethical commission (Commission Centrale d'éthique de la Recherche des Hôpitaux

Universitaires de Genève). From the initial sample of 123 adolescents, 13 adolescents were excluded to ensure a psychologically and medically healthy sample, as they were diagnosed with: depression and anxiety disorders (n=8), attention-deficit hyperactivity disorder (ADHD, n=4) or schizoaffective disorder (n=1). None of our participants was taking psychoactive treatment, see *supplementary material Appendix 4* for more information.

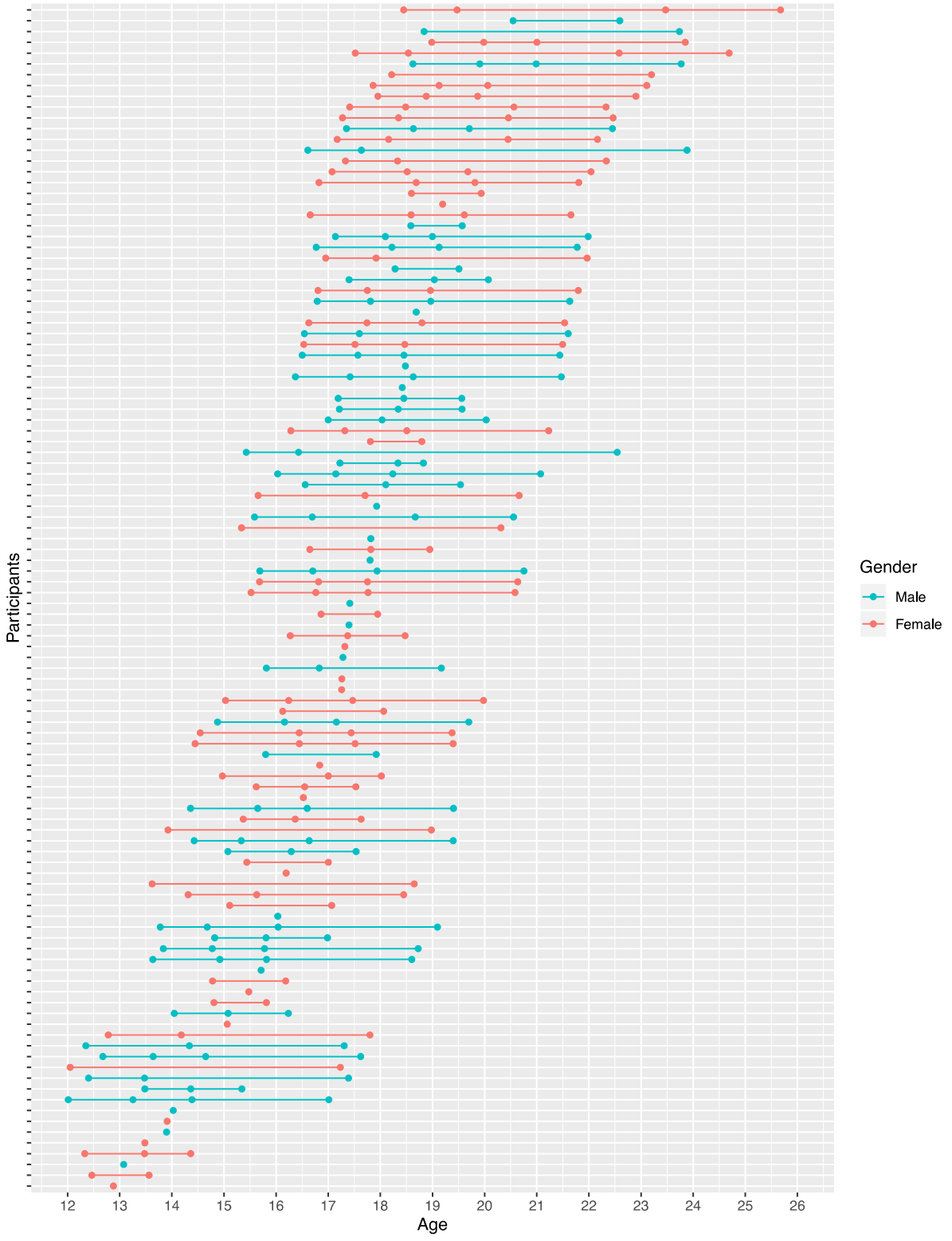


Figure 9 Age distribution of participants

Psychological Measures

To isolate the effect of schizotypy on subcortical structures development, we covaried for potential effects of internalized and externalized maladaptive behaviors (G. Modinos et al., 2014). To do so we included the Youth Self Report and Adult Self Report (YSR/ASR) standardized subscale scores of externalizing and internalizing behaviors as covariates in the neuroimaging statistical analyses.

Schizotypal personality traits were evaluated with the SPQ, which define 3 dimensions (positive, negative and disorganized - see *supplementary material Appendix 4* for details on these measures).

Partition of participants in groups

Higher and Lower groups of participants were created based on their SPQ score at first time point for each dimension separately (positive, negative and disorganized) in order to assess the potential influence of each of them on the development of subcortical volumes. For each dimension, optimal k-means clustering for univariate data implemented in R (ck.means.1d.dp package) was conducted (see *supplementary material Appendix 4* for details). According to the Bayesian criterion the algorithm returned 2 clusters as the best option per dimension: one representing the adolescents with elevated scores and the second one concerning individuals with low scores on a dimension: high positive scorers (HPS) and low positive scorers (LPS), high negative scorers (HNS) and low negative scorers (LNS), high disorganized scorers (HDS) and low disorganized scorers (LDS).

MRI acquisition

Magnetic Resonance Imaging (MRI) scans were acquired on a 3-Tesla Siemens Trio scanner at the Hôpitaux Universitaire Genevois (HUG, n=228), or at the Brain Behavioral Laboratory at University of Geneva (BBL, n=81). Both sites used the same scanner and sequences of acquisition. A 3D volumetric pulse sequence was used, with the following parameters: TR = 2500 ms, TE = 3 ms, flip angle = 8°, acquisition matrix = 256 x 256, field of view = 22 cm, slice thickness = 1.1 mm, 192 slices.

MRI processing

To obtain an accurate three-dimensional cortical model, images were processed using *FreeSurfer* software version 6.0 (http://surfer.nmr.mgh.harvard.edu). Processing steps were conducted following the *Freesurfer* pipeline for fully automated preparation of images, including resampling of the surface into cubic voxels, skull stripping, intensity normalization, white matter segmentation, surface atlas registration, surface extraction and gyrus labeling. After preprocessing, each participant was registered to the spherical atlas *fsaverage* in *FreeSurfer*. For each individual, resulting white matter and pial surfaces were visually checked and manually corrected when necessary.

MRI Longitudinal processing

In order to reduce within subject variability between scan sessions, a longitudinal analysis methodological step was performed using FreeSurfer version 6.0. This method increases

repeatability and statistical power (Reuter et al., 2012). All scans were processed using this procedure, including individuals with a single time point to ensure consistency of treatment for all scans (Bernal-Rusiel et al., 2013). An unbiased within-subject template and average image were created, using inverse consistent registration. This reduces the potential over-regularization of longitudinal image processing (Reuter et al., 2010).

Subcortical volumes extraction

Left and right thalamus, lateral ventricle, pallidum, accumbens, caudate, putamen, hippocampus, amygdala volumes as well as intra cranial volumes (ICVs) were obtained from the T1 pre-processed scans (see Figure 10), using FreeSurfer and following the Enigma protocol for extraction of volumes' values **(**enigma.usc.edu) (Stein et al, the Alzheimer's Disease Neuroimaging Initiative (ADNI), 2012). For quality control, all regions of interest (ROIs), with a volume larger than or <1.5 times the interquartile range were identified and visually inspected by overlaying their segmentation on the subjects' anatomical images. ROI data for which segmentation was judged accurate were included in statistical analyses (van Erp et al., 2016), no scans had to be excluded.

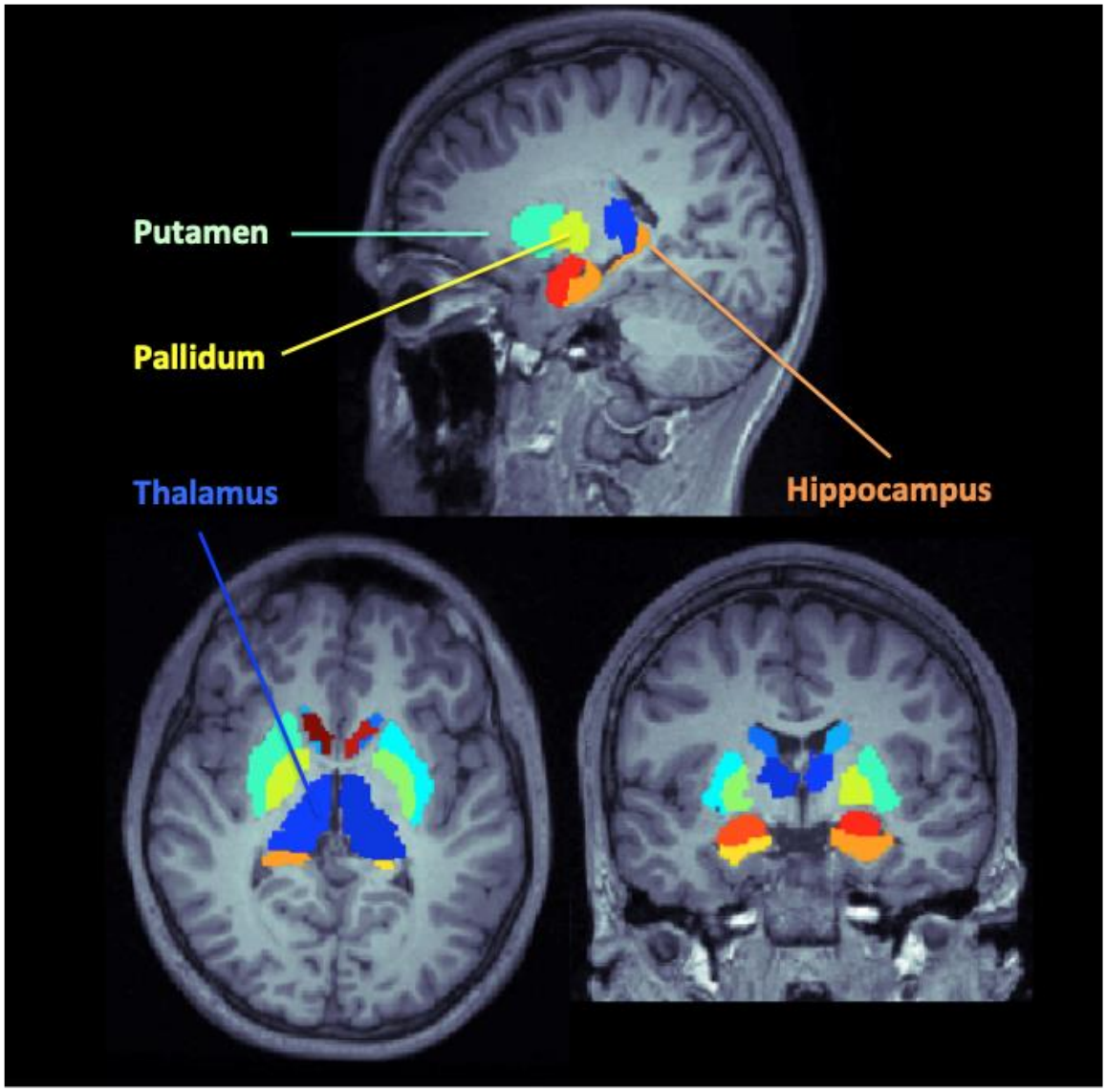


Figure 10: Segmentation of the different subcortical structures (Freesurfer version 6.0)

Statistical analyses: descriptive statistics

We performed descriptive analyses comparing participant within subgroups statistics as obtained with the schizotypy clustering methodology using Mann-Whitney U tests in SPSS

version 24.0 to compare Age and cognitive variables (ASR/YSR internalized and externalized behaviors and WISC/WAIS-IV block design standardized scores). We used chi square tests to compare sex and scan locations between groups.

Statistical MRI analyses: Developmental trajectories

We performed mixed model regression analyses to examine developmental trajectories of subcortical volumes, the potential differences between high and low levels of each schizotypy dimensions, as well as the interaction between schizotypy dimensions and age. Following a previously published procedure (Mancini et al., 2019b), we fitted random-slope models to our data to estimate optimal developmental trajectories considering both within-subject and between-subject effects. Briefly, the *nlmefit* function in MATLAB R2016b was used to estimate constant, linear, quadratic and cubic models. Then, the best model was selected based on the Bayesian Information Criterion (H. Peng & Lu, n.d.). All models included group, age, and their interaction as fixed effects. Finally, a likelihood ratio test was used to quantify significant between-group differences in the intercept and slope of resulting developmental trajectories. To perform these analyses we used in-house scripts that have been made available at https://github.com/danizoeller/myMixedModelsTrajectories.

For each analysis, sex, location of MRI scanner, ASR/YSR internalized and externalized behaviors score, ICVs, as well as Wechsler's WISC/WAIS-IV Block Design standardized score were entered as mean-centered (demeaned) covariates of no interest. We analyzed left and right hemisphere separately, and all retained results survived a threshold of $p<0.05$, corrected for multiple comparisons using False Discovery Rate FDR.

Results

Descriptive statistics

Are presented in Table 5 for each group of high and low scorers on the three dimensions of schizotypy. The low positive schizotypy group comprised 76 individuals and the high positive scorers consisted of 34 adolescents. The negative schizotypy groups included 68 low scorers and 42 high scorers. Lastly, the group based on the disorganized dimension consisted of 74 low scorers and 36 high scorers. All pair of groups (high VS low) differed in terms of schizotypy scores as well as internalized behaviors but not on age, block design and vocabulary subtest. Additionally, low and high positive and disorganized scorers differed on externalized mean scores.

Variable	LPS		HPS		Sig.		LNS		HNS		Sig.		LDS		HDS		sig	
N (Total = 110)	76		34				68		42				74		36			
Gender (%)	30 F (39.4)		23 F (67.6)		**		22 F (32.3)		31 F (73.8)		***		30 F (40.5)		23 F (63.8)		n.s	
Number of scans (n=297)	208		89				183		114				191		106			
Scan Location	Site1(n=155) /site 2 (n=53)		Site1(n=62) /site 2(n=27)		n.s		Site1(n=131) /site 2(n=52)		Site1(n=86) /site 2(n=28)		n.s		Site1(n146=) /site 2(n=45)		Site1(n=71) /site 2(n=35)		n.s	
	Mean	SD	Mean	SD	Sig.	g	Mean	SD	Mean	SD	Sig.	g	Mean	SD	Mean	SD	Sig	g
Age	16.04	1.8	16.01	1.9	n.s		16.22	1.77	15.73	1.92	n.s		16.01	1.87	16.06	1.8	n.s	
SPQ positive	5.01	2.9	17.59	5.3	***	2.9	6.78	5.5	12.33	7.7	***	0.8	6.18	4.96	14.5	7.3	***	1.43
SPQ negative	5.16	4.0	8.38	4.4	***	0.76	3.32	2.21	10.74	2.89	***	2.98	5.22	3.98	8.08	4.6	**	0.68
SPQ disorganized	4.47	3.2	8.59	3.4	***	1.2	4.5	3.4	7.76	3.4	***	0.9	3.58	2.21	10.19	2	***	3.06
ASR/YSR Internalizing	49.47	9.6	58.56	9.29	***		47.57	8.6	59.9	8.27	***		50.11	9.54	56.75	11	**	
ASR/YSR Externalizing	54.53	9.6	59.23	8.7	*		54.71	10	58.05	8.1	n.s		54.62	9.94	58.78	8.3	*	
WISC/WAIS (Block Design)	10.84	3.1	9.59	3.13	n.s		10.19	3.22	10.88	3.05	n.s		10.49	3.34	10.39	2.8	n.s	
WISC/WAIS (Vocabulary)	11.23	3.4	11.42	2.43	n.s		11.5	2.9	10.95	3.4	n.s		11.48	3.3	11	2.9	n.s	

Table 5: Descriptive statistics of groups based on positive, negative and disorganized dimension

Developmental trajectories

Significant results of the mixed models analyses for each ROI are shown in *supplementary Table 2* (all results can be found in *appendix 4*). No significant results were found when investigating the positive dimension. We observed differential linear developmental trajectories in four subcortical structures when comparing higher scorers on the disorganized and negative dimensions of schizotypy to their respective lower scorers. We showed trajectories of results that were significant at $p<.05$, corrected for multiple comparisons using the FDR criterion (see Figures 11&12).

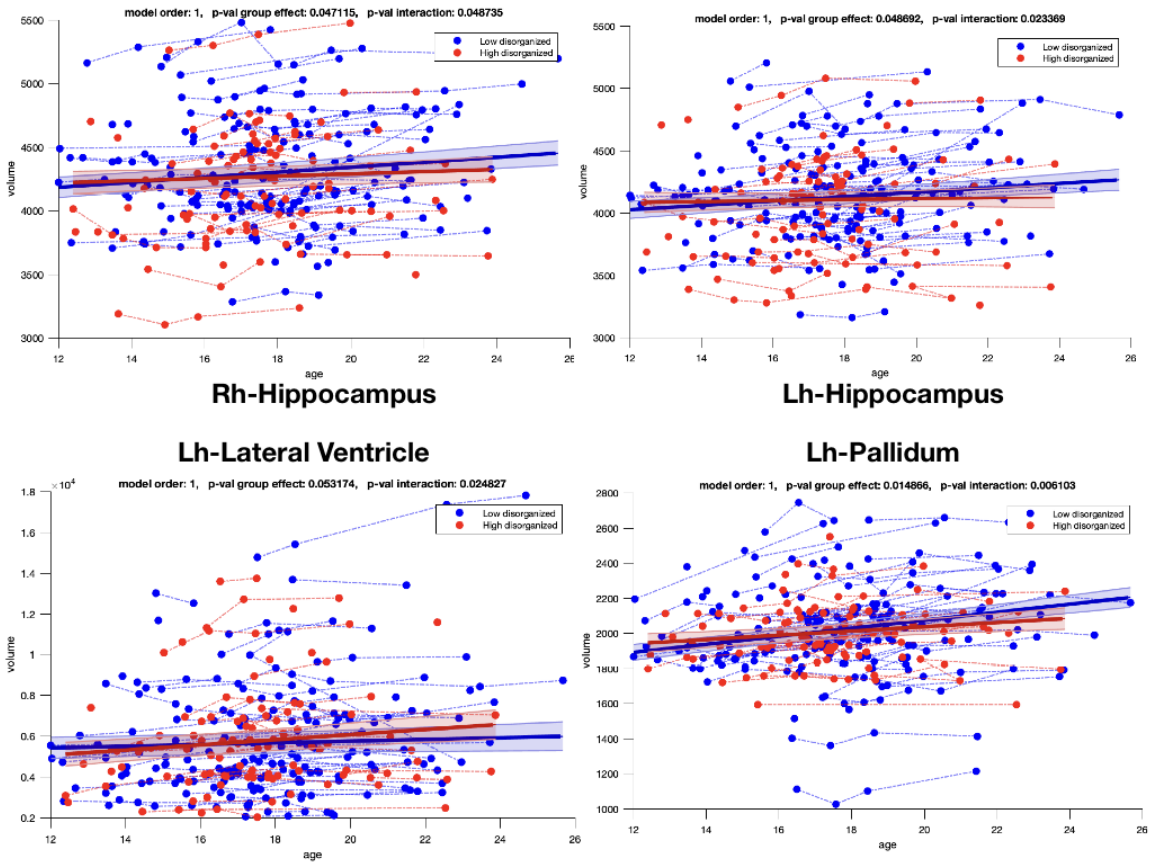


Figure 11: Developmental trajectories of high versus low Disorganized schizotypy

Disorganized dimension (Figure 11)

Adolescents expressing higher levels of *disorganized* schizotypy (HDS) exhibited a steady developmental trajectory of bilateral hippocampus volumes, whereas LDS showed a linearly increasing volume trajectory. Notably, after 17 years of age LDS showed steeper increasing volumes trajectory of both right and left hippocampus when compared to HDS (R-hippocampus: p=0.049; L-hippocampus: p=0.023).

We found a similar pattern concerning the left pallidum with LDS showing a steeper increasing trajectory than HDS. Both trajectories followed a linear increase, however the enlargement trajectory was more pronounced in LDS (p=0.006).

Concerning the left lateral ventricle (p=0.025), we found the opposite pattern, with a steeper linearly increasing trajectory in adolescents who scored higher on disorganized schizotypy. Once again, the trajectories seem to cross at 17 years old, the LDS group followed a relatively constant trajectory, whereas after this age, the lateral ventricle in the HDS group showed a steeper enlargement.

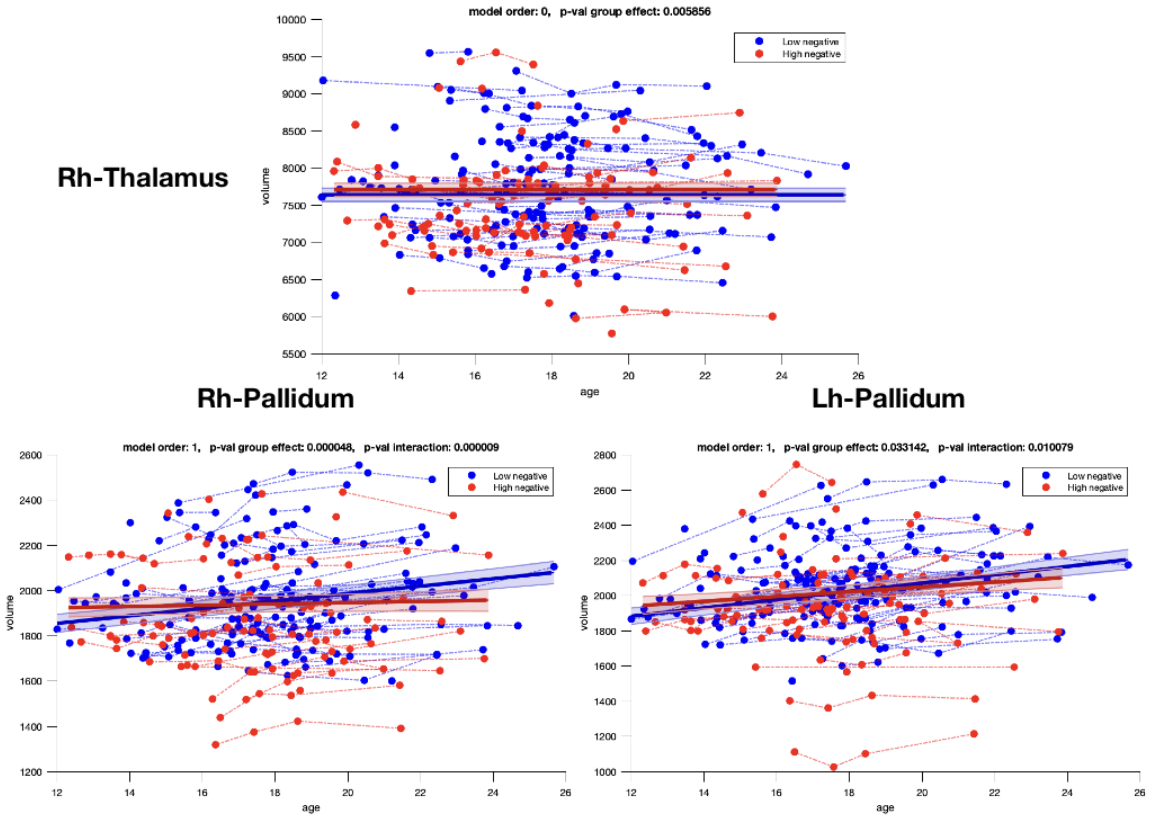


Figure 12: Developmental trajectories of high versus low Negative schizotypy

Negative dimension (Figure 12)

Concerning the *negative* dimension of schizotypy, lower scorers presented a stronger linearly increasing trajectory of bilateral pallidum volumes (right-pallidum: $p<0.000$; left-pallidum: $p=0.010$) when compared to HNS. Once again, we observed a change around 17 years of age, where HNS exhibited lower rate of increasing volumes than LNS passed this age.

When looking at the right thalamus (group effect, $p=0.006$), we identified similar patterns of developmental volume trajectories. Both HNS and LNS had constant trajectories, and volumes were larger in HNS than LNS throughout the entire investigated age range.

Discussion

We investigated the developmental trajectory of subcortical brain structures in adolescents expressing higher schizotypal traits compared to matched adolescents without such traits. Importantly, with our adolescents coming on a voluntary basis from the general population, we measured a mild variant of schizotypal features less pronounced than in clinical samples. However, our strategy was to focus on the developmental antecedents of the clinical states that can ensue during adulthood. We observed differential linear trajectories in four different subcortical structures when comparing higher disorganized and higher negative dimension scorers to their corresponding lower scorers. Expression of higher level of disorganized schizotypy was associated with differential trajectories of the hippocampus bilaterally, the left pallidum and lateral ventricle. On the other hand, higher levels of negative schizotypy were associated with differences in trajectories within the pallidum bilaterally, and with globally reduced volumes over the entire age range in the thalamus. With the present longitudinal study,

we sought out to characterize which subcortical volumes differences were associated with a vulnerability to develop schizophrenia spectrum disorders to those linked to inter-individual variability of the schizotypy trait and/or a compensatory process. Convergence with findings in clinical populations, notably CHR-converters may be indicative of processes involved in pathogenesis, but divergence may be indicative of protective/resilience factors or variability in term of personality traits.

[Reduced volumes of hippocampus are observable in relation to disorganized schizotypy]

Previous research consistently reports that hippocampus volumes are significantly reduced in schizophrenia patients (Huang et al., 2015; Spoletini et al., 2011), as well as in their non-psychotic relatives (Bois et al., 2016). In addition, longitudinal studies have provided evidence for progressive reductions in the hippocampus of individuals at clinical high risk compared to controls, suggesting that alterations to this structure may form part of a general vulnerability to schizophrenia (Pantelis et al., 2003; Walter et al., 2012). In the present study, high scorers on disorganized schizotypy were lacking a developmental increase that was present in low scorers, leading to a tendency for reduced hippocampal volumes at the end of adolescence. This suggests a similarity with schizophrenia spectrum disorders, and notably with individuals at clinical high risk of developing psychosis, thus representing a potential vulnerability feature. Reinforcing this idea, CHR participants who subsequently convert to psychosis are reported to show hippocampal hypermetabolism which predicts hippocampal volume loss (Schobel et al., 2009). On the other hand, the increasing developmental trajectory observed in the lower scorers is in line with previous research indicating a robust maturational process in healthy individuals resulting in linear increase of hippocampal volumes along adolescence (Gogtay et al., 2004; Suzuki et al., 2004; Giedd et al., 1996). As similar longitudinal abnormalities of

hippocampal volumes are observable in CHR individuals, they could potentially represent an increased predictive risk to develop psychosis rather than being specific to illness-related mechanisms.

[Enlargement of lateral ventricle is associated with disorganized dimension of schizotypy]

Enlarged volume of left-lateral ventricle found in adolescents with HDS are concordant with large scale studies of schizophrenia (Okada et al., 2018; van Erp et al., 2016), FEP (Ellison-Wright et al., 2008) patients, as well as in adolescents with SPEs (Okada et al., 2018). However, in FEP patients, some contradiction exist, as longitudinal studies have showed a progressive enlargement occurring after the first episode and especially within the first years of illness (Kempton et al., 2010). Thus, the question arises whether ventricular dilation was a progressive change beginning in the prodromal phase of the illness, or an abnormal developmental process starting closer to birth with progressive changes through life. Our results lend support to the latter hypothesis suggesting that ventricular enlargement seems to be progressive, and present at the earliest stages of the spectrum as it is already observable in adolescents expressing higher levels of disorganized schizotypy. Opposite findings in favor of the prodromal-start to enlargement could be explained in terms of modulation of trajectories by psychotic episodes, periods of remission and antipsychotic treatment (Garver & Kingsbury, 2000).

[Decreased volume of the pallidum was found in relation to disorganized and negative dimension]

The pallidum, enlarged in chronic schizophrenia (Okada, 2016) was found to be decreased in our study in HDS (left-pallidum) as well as in HNS (bilateral pallidum) when compared to their respective low scorers. However, normal pallidal volumes were demonstrated in drug-naïve

(Spinks et al., 2005) schizophrenia patients, FEP (Lang et al., 2001) and CHR (Harrisberger et al., 2016). Our results concerning the trajectory of low scorers on both dimensions follow a linearly increasing trajectory that resemble the first part of the typical inverted U shaped trajectory found in healthy adolescents (Wierenga et al., 2014). Therefore, we could suggest that the subtle volumetric decrease exhibited in higher scorers may only reflect inter-individual variability. Moreover, pallidum alterations did not seem to be specifically linked with the negative or disorganized dimension of schizotypy, whereas they were found to be associated with processing speech alterations and negative symptoms in patients with schizophrenia (Mwansisya et al., 2013).

[Increased thalamic volumes are observable in high negative schizotypy]

Studies involving typical adults have observed a trend (no correction for multiple comparison) of negative association between schizotypy total score and thalamic volumes (Kühn et al., 2012), compatible with reports of thalamic volume reductions in samples of individuals with schizophrenia (Ettinger et al., 2001), FEP (Adriano et al., 2010) and antipsychotic-naïve CHR (Harrisberger et al., 2016). In contrast, in the present study, adolescents expressing higher level of negative schizotypy presented increased volumes of the thalamus when compared to lower scorers, consistent with the inverted U-shaped developmental trajectory observable in typically developing children and adolescents (Wierenga et al., 2014) (7 to 24y.o). Those differences may be explained in terms of age, as our population included only adolescents, as well as by the fact that we studied the dimensions separately. Moreover, it is not clear whether reduced thalamic volumes documented by imaging studies pertains to any specific nuclei of the thalamus. In the literature the question also arises whether thalamic reductions may represent an intermediate phenotype of presumed inherited vulnerability to schizophrenia (Allen et al.,

2009). Thalamic structural volume decreases are observable early in the CHR population, but not in typical adolescents expressing higher level of negative schizotypal traits. Thus, we could also hypothesize that structural abnormalities of the thalamus might be subsequent to negative symptoms expression.

[Limitations]

Some limitations should be acknowledged. First, we looked at the whole volume of the different subcortical structures, rather than the substructures that compose them. Secondly, we included the whole period of adolescence, however, pubertal stages are known to greatly influence the development of subcortical structures, and therefore it could be promising to consider only the prepubertal stage. Secondly, we used a self-rated instrument (SPQ) to measure schizotypy; future studies should include an observer rater (i.e. interviews). While longitudinal schizotypal traits studied in the general population are still a burgeoning field, further research using larger cohorts is required. We contend that enhanced longitudinal characterization (with more time points or following the converters to psychosis) will prove fruitful grounds for replication and for discovering developmental processes that may be used as risk markers of impending disorders.

[Conclusion]

We described developmental trajectories of a number of subcortical structures using mixed model regression longitudinal analyses in a population of typically developing adolescents. Moreover, we identified disorganized personality traits of schizotypy associated with developmental trajectories of subcortical volumes and found similar pattern than those identified along the schizophrenia spectrum, notably the hippocampus and lateral ventricle.

Higher levels of disorganized schizotypy identified during adolescence seemed to be linked to subtle developmental changes reflecting a neural signature at the non-clinical level. We additionally identified differences in trajectory patterns to those seen along the spectrum, notably decreased pallidum and increased putamen volumes which should be further investigated in clinical population to be interpreted as potential protective compensatory factors.

3. Study 3 – A developmental study of mirror gazing-induced anomalous self-experiences and self-reported schizotypy from 7 to 28 years of age

Abstract

The mirror-gazing task (MGT) is an experimental paradigm inducing anomalous perceptions and anomalous experiences of self-face (ASEs) in the general population, ranging from changes in light and color, to face deformation, to experiencing one's specular image as another identity. Subclinical ASEs have been related to the emergence of the risk for developing psychotic disorders and inducing such states in the general population could shed light on the factors underlying interindividual differences in proneness to these phenomena. We aimed to examine the influence of schizotypal personality traits on proneness to experiencing induced ASEs from a developmental perspective, from childhood to adulthood. Two hundred and sixteen children, adolescents, and young adults participated in the MGT, and their schizotypal personality traits were assessed with the Schizotypal Personality Questionnaire. Statistical analyses assessed the relationship between schizotypy dimensions and induced ASEs, and we further tested their dynamic relationship as function of age (children vs adolescents vs adults). Results confirmed the developmental trajectory of the different schizotypy dimensions, with scores peaking during adolescence, and proneness to induced ASEs seemed to follow a similar developmental trajectory. Moreover, positive (P=0.005) and disorganized (P=0.011) schizotypal personality traits were found to contribute to the proneness to experiencing induced ASEs. Finally, the developmental model showed that positive schizotypy ($P_{Bonferroni}$=0.013) uniquely distinguished between experiencing other-identity phenomena between childhood and adolescence. This study has the potential to inform research on early detection of psychosis

through a developmental approach and links the concept of schizotypy with processes of perceptual self-distortions.

1. Introduction

Individuals on the spectrum of psychotic disorders have reported sometimes experiencing facial distortions of their own specular image in the mirror (Harrington et al., 1989). This uncanny mirror phenomenon can be conceptualized as a specific subtype of anomalous self-experiences (ASEs), which are defined as a broad range of subtle disturbances of the self (including cognition, thoughts, affect, and perception). Research suggests that self-disturbances can, in some cases, precede "surface-level" anomalous perceptual experiences such as hallucinations, and carry a risk/vulnerability for developing psychotic spectrum disorders (Raballo & Parnas, 2011).

Most contemporary research on subjective self-experiences relies on clinical interviews, but these experiences are often subtle, difficult to conceptualize, quantify, and verbalize, and they may be forgotten. The present study aims to investigate perceptual self-experiences through an experimental paradigm that can induce a momentary state of perceptual distortion akin to symptoms of self-disturbances observable in high-risk states. We propose an alternative way of studying such phenomena, through the experimental induction of such states using a methodology consisting of partial sensory deprivation. Among such experimental procedures, one that examines apparitional experiences and perceptual visual illusions during mirror gazing, the mirror-gazing task (MGT), was initially proposed by Caputo and colleagues (Caputo, 2010; Caputo et al., 2012). When confronted with the MGT, participants with

schizophrenia reported that they experienced strange facial apparitions during the task more intensely and more frequently than healthy controls, with 50% of patients reporting archetypal face (vs 19% for controls) and 88% reporting monstrous faces (vs 29% for controls, (Caputo et al., 2012b)). In a group of 50 healthy young adults, 66% reported seeing another identity, including monstrous face (48%), unknown person (28%), archetypal face (28%), relative (18%), and animal face (18%) (Caputo, 2010). Fonseca-Pedrero and colleagues validated the MGT in a community sample of 110 adolescents, of whom 35% reported seeing an identity other than themselves in the mirror (27.3% experienced another human identity, and 7.3% experienced a non-human identity)(Fonseca-Pedrero et al., 2015).

Few studies to date have attempted to identify factors sustaining interindividual differences outside the clinical states, which is crucial to understand whether and why some people are more prone than others to experiencing induced perceptual distortions of the self. The construct of schizotypy, through its links to personality theories and early detection accounts of psychosis (Debbané et al., 2016), may partly account for interindividual differences in the propensity to experience perceptual distortions. Schizotypy is defined as the behavioral expression of latent vulnerability to psychotic disorders (Linscott & van Os, 2013). Studying schizotypy in healthy individuals provides the advantage of bypassing the potential effects of comorbidities, hospitalization, and medication that are present in samples of participants with clinical disorders. There is a general consensus that schizotypy follows a heterogeneous multidimensional structure similar to that found on the schizophrenia spectrum, with a triad of positive (cognitive perceptual), negative (interpersonal), and disorganized dimensions (Raine et al., 1994; Fonseca-Pedrero et al., 2009; Nelson et al., 2012; Barrantes-Vidal et al., 2015; Cicero, 2016; Davidson et al., 2016; Fonseca-Pedrero et al., 2018).

In 2015, Fonseca-Pedrero and colleagues examined specifically adolescents experiencing their specular image as that of someone else, targeting phenomena of momentary depersonalization of the specular image, a kind of experimentally induced dissociative state. They showed that these adolescents who experienced dissociation of self-identity on the MGT presented with higher positive and disorganized self-reported schizotypy (Fonseca-Pedrero, et al., 2015). Furthermore, a previous study from our laboratory conducted in typically developing adolescents confirmed the link between proneness to induced ASEs and higher levels of positive and disorganized self-reported schizotypy (Derome et al., 2018). Furthermore, in the same study, we reported on the neural signature in adolescents experiencing depersonalization-like phenomena, characterized by atypical connectivity within the default mode and primary visual networks, and found that the persistence of such phenomena after 1 year was sustained by disorganized schizotypy. These previous studies underlined the relationship between MGT-induced self-distortions and self-reported schizotypal traits (Derome et al., 2018; Fonseca-Pedrero, et al., 2015; Nordgaard & Parnas, 2014), suggesting that schizotypy increases the proneness to experiencing task-induced ASEs during adolescence at the behavioral and neural levels.

Following the studies previously reviewed and the absence of research on children, we will investigate the propensity of experiencing ASEs in relation to age from childhood to young adulthood. The overarching goal of this study is to chart the developmental trajectory of proneness to strange face illusions from ages 7 to 28 years and investigate the dynamic relationship with schizotypal personality traits. Taking into consideration the fact that adolescence is a period of major change for both personality traits and self-development, we

postulate that adolescents will be more prone to experiencing ASEs as induced with the MGT than children and adults. Secondly, we want to confirm the relationship between proneness to MGT-induced ASEs and self-reported positive and disorganized schizotypy. Lastly, we will evaluate different potential inverted U-shaped developmental trajectories (from 7 to 28 years of age), including the links between self-reported schizotypy, age group (children vs adolescents vs adults), and MGT-induced ASEs.

2. Methods

2.1 Participants

Two hundred and fifty-three participants were recruited from the community through advertising leaflets and by word of mouth and were tested in our research facilities at the University of Geneva. We tested children (aged between 7 and 12 years), adolescents (aged between 13 and 17 years) and young adults (between 18 and 30 years old). These age ranges were selected considering that adolescence was related to pubertal stage), and in accordance with World Health Organization guidelines: (https://apps.who.int/adolescent/second-decade/section/section_2/level2_2.php). Thirty-four participants were excluded because of missing data on questionnaires (n=16), because they did not perform the task (n=11), or because of missing demographic data (n=7). An additional three participants were excluded as they were outliers in terms of age (one was too young and two were too old in comparison to the rest of the sample).

The study sample included 216 participants and comprised 68 children (34 females and 34 males, age range 7.85 to 12.96 years, M=10.7, SD=1.45), 86 adolescents (53 females and 33 males, age range 13.04 to 17.96 years, M=16.5, SD=1.46), and 62 young adults (34 females

and 28 males, age range 19.31 to 27.94 years, M=24.6, SD=2.23). The sample included 70.8% white Caucasian, 5% other (African, Asian) and 23.6% mixed (i.e. Franco-Suisse, Suisse-Italian, Indian-European, Italian-English) participants. They were primarily of higher socio-economic status as graded in terms of their parents' occupational category: 51% of parents were management and senior executives, 13% were academics and scientific professionals, 7.9% worked in intermediate professions, 6% were administrative employees, 11% were customer service and sales personnel, 6.9% were farmers, hunters (etc.), 1.8% were machine and industrial robot operators, and less than 1% were workers and unskilled workers.

To be eligible to participate in the study, participants needed to be aged between 8 and 30 years, French native speakers, and, for those younger than 16 years, to have received parental consent to participate. Written informed consent was received from participants and/or their parents under protocols approved by the Institutional Review Board of the Department of Psychology and Educational Sciences of the University of Geneva.

2.2 Instruments

All instruments and experimental tasks were administered on the same day for each participant.

For adult and adolescent participants, schizotypal personality traits were assessed with a validated French-language version of the Schizotypal Personality Questionnaire (SPQ) (Badoud et al., 2011). The SPQ consists of a 74-item self-report questionnaire (Fonseca-Pedrero et al., 2008, 2014; Ortuño-Sierra et al., 2013). The positive dimension combines the following subscales: ideas of reference, odd beliefs or magical thinking, unusual perceptual experiences, and suspiciousness. The negative dimension includes the subscales constricted affect, excessive social anxiety, and having no close friends. The disorganized schizotypy dimension encompasses the subscales odd or eccentric behavior and odd speech. The

psychometric properties of the SPQ have been widely assessed in adult and adolescent populations (Fonseca-Pedrero et al., 2018) .

The SPQ-child (SPQ-C) version (Raine et al., 2011) was administered to the group of children. The SPQ-C is a downward extension of the adult SPQ-brief, which is itself a short form of the full SPQ. The SPQ-C consists of 22 items, which have yes/no answers, and contains all the items from the SPQ-B with minor modifications for use with children aged between 8 and 16 years. The questionnaire provides scores for total schizotypy as well as the three subfactors of cognitive-perceptual, interpersonal, and disorganized schizotypy. The SPQ-C was translated and adapted into French following the International Test Commission (2017) guidelines for translating and adapting tests. Results of the reliability analysis in the sample included in the present study yielded a Mc Donald ω (Şimşek & Noyan, 2013) of 0.75 for the cognitive-perceptual subscale (items 2, 4, 5, 7, 9, 10, 12, 14, 16, and 17), 0.73 for the interpersonal subscale (items 1, 7, 9, 11, 14, 15, 17, 18, 21, and 22), and 0.78 for the disorganized subscale (items 3, 6, 8, 13, 19, and 20). The SPQ-C version has shown adequate psychometric properties in previous studies (Fonseca-Pedrero et al., 2009; Liu et al., 2019; Raine et al., 2011).

The MGT has already been employed in a sample of adolescents in our research unit and is described in previous reports (for details of the task, see (Derome et al., 2018)). Briefly, participants were asked to stare at themselves for 10 minutes in a mirror placed 40 cm away from their eyes. The room in which the test was conducted was lit only with a halogen bulb (12 V, 20 W) mounted on a spotlight and placed 1.2 m behind the participant. Two independent raters (M.D. and M.D., Kappa coefficient of 0.75) assessed the qualitative answers of the post-mirror task questionnaire, which was administered in French at the end of the 10 minutes. For the present study, we used the following questions (either yes/no questions followed by description, or descriptive questions): During the task have you “noticed a change in light, color or contrast? If yes please describe”; “Did you see another person in the mirror? If yes

please describe"; "Please provide a listing of all types of modifications you saw during the task". With the children, the experimenter made sure that each participant understood the task correctly by asking them to re-explain the instructions. The questionnaire was filled in by the experimenter, who clarified any terms that were not understood by the participant. Based on the MGT, we classified participants into three different groups depending on their qualitative visual experiences. The first group included participants who perceived changes in light, color, or contrast; the second group contained participants who experienced deformations of their own faces; and the third group consisted of participants who reported seeing another facial identity (either human or non-human). Individuals were classified into one of these groups on the basis of the most significant illusion they reported.

2.3 Statistical analyses

All analyses were conducted using JAMOVI software (https://www.jamovi.org/). For each analysis, gender (coded as a dummy variable) was introduced as a covariate in order to isolate the effect of variables of interest except for Kruskal–Wallis tests, which did not allow the inclusion of covariates.

2.3.1 Age comparison: schizotypy dimensions and MGT

Comparisons of self-reported schizotypy between the different age groups were conducted using Kruskal–Wallis tests to compare the three self-reported schizotypy dimension scores between the child, adolescent, and adult groups. The three SPQ dimensions (positive, negative, and disorganized) were entered as individual dependent variables, and age group (coded: 1=children, 2=adolescents, 3=adults) was entered as the fixed variable. As an estimate of effect size, epsilon squared (ε^2) were employed. Dwass–Steel–Critchlow–Fligner pairwise comparisons were used for post-hoc testing.

For the comparison of propensity to experience MGT-induced ASEs between age groups, a log linear regression was used to statistically compare the distribution (counts) of belonging to the three age groups versus belonging to the three MGT groups (as described above: 1) light/color, 2) deformation of own face, 3) other identity). The overall effect was first tested, followed by the underlying differences between pairs of groups

2.3.2 Relationship between self-reported schizotypy dimensions and propensity to experience MGT-induced ASEs

The Kruskal–Wallis test was used to compare the three self-reported schizotypy dimension scores between the three MGT groups. Schizotypy dimensions were entered as three dependent variables, and the MGT groups as the grouping variable (coded: 1= light/color, 2=own face deformation, 3=other identity). As an estimate of effect size, ε^2 were employed. Dwass–Steel–Critchlow–Fligner pairwise comparisons were used for post-hoc testing.

2.3.3 Integrative model of self-reported schizotypy, age groups, and propensity to experience MGT-induced ASEs

Associations of self-reported schizotypy dimensions as well as age group and propensity to experience MGT-induced ASEs were examined with generalized linear models. According to their graphs and the Akaike information criterion, we fitted models of Gaussian distribution with an identity-link function for both age and MGT groups. We modelled the parameter estimate “age group” as polynomial (which added a linear and quadratic definition of the age group variable) as we hypothesized that proneness to induced ASEs would follow a similar trajectory to schizotypy traits with age, peaking during adolescence and then reducing in

adulthood to yield a non-linear relationship (inverted U-shaped trajectory). The parameter estimate "MGT group" was modelled as simple. Post-hoc comparison tests were performed, and significant results were retained for $p<0.05$ corrected using Bonferroni correction for multiple comparison.

3. Results

3.1 Descriptive statistics for schizotypy dimensions between age groups

Statistically significant differences in self-reported schizotypy between the three age groups (children vs adolescents vs adults) were found for the three dimensions of schizotypy (positive, $\chi^2 = 91$, $p<0.001$, $\varepsilon^2=0.431$; negative, $\chi^2 = 54.3$, $p<0.001$, $\varepsilon^2=0.258$; disorganized, $\chi^2 = 48.5$, $p<0.001$, $\varepsilon^2=0.230$). Results are shown in Appendix 5. Pairwise comparison between age groups showed that the positive dimension differed as follows: children<adults<adolescents. Concerning the disorganized dimension, scores differed significantly between children and adolescents (children<adolescents) and between adolescent and adults (adolescents>adults). Finally, the negative dimension differed significantly between children and adolescents (children<adolescents) and between adolescents and adults (adolescents>adults).

3.2 Comparison of the propensity of experiencing ASE between age groups

The following types of strange face illusions were observed in our sample: 17.1% (n=37) reported seeing a slight change of light and color (of whom 54.1% were children, 21.6% were

adolescents, and 24.3% were adults), 47.2% (n=102) experienced deformations of their own faces (of whom 25.5% were children, 44.1% were adolescents, and 30.4% were adults), and 35.6% (n=77) reported seeing another facial identity (of whom 28.6% were children, 42.9% were adolescents, and 28.6% adults); see Table 6 and Figure 13.

The overall log linear model was significant (χ^2=47.7, p<0.001; see Appendix 5), specifically yielding main effects for age group and MGT group factors, as well as a statistically significant interaction between MGT group and age group (χ^2=11.07, p=0.026; see Appendix 5). Model coefficients testing was mostly explained by differences in the frequency between children and adolescents in the groups light/color and own face deformation (Z=–3.017, p=0.003) and in the groups light/color and other identity (Z=–2.64, p=0.008); see Table 7.

Contingency Tables

MGT Group		Age group			Total
		Children	Adolescents	Adults	
Light/Color	Observed	20	8	9	37
	% within row	54.1%	21.6%	24.3%	100.0%
	% within column	29.4%	9.3%	14.5%	17.1%
Own face deformation	Observed	26	45	31	102
	% within row	25.5%	44.1%	30.4%	100.0%
	% within column	38.2%	52.3%	50.0%	47.2%
Other ID	Observed	22	33	22	77
	% within row	28.6%	42.9%	28.6%	100.0%
	% within column	32.4%	38.4%	35.5%	35.6%
Total	Observed	68	86	62	216
	% within row	31.5%	39.8%	28.7%	100.0%
	% within column	100.0%	100.0%	100.0%	100.0%

Table 6: Frequency of self-reported experiences of various types of illusions in different age groups, children vs adolescents vs adults.

Model Coefficients

Predictor	Estimate	SE	Z	p	Rate ratio
(Children – Adolescents) × (Own face deformation – Light/Colors)	-1.465	0.485	-3.017	0.003	0.231
(Adults – Adolescents) × (Own face deformation –Light/Colors)	-0.490	0.539	-0.910	0.363	0.612
(Children – Adolescents) × (Other ID) –Light/Colors)	-1.322	0.501	-2.640	0.008	0.267
(Adults – Adolescents) × (Other ID) –Light/Colors)	-0.523	0.558	-0.937	0.349	0.593

Table 7: Statistical analyses of various types of illusions in different Age group, Children vs Adolescents vs Adults.

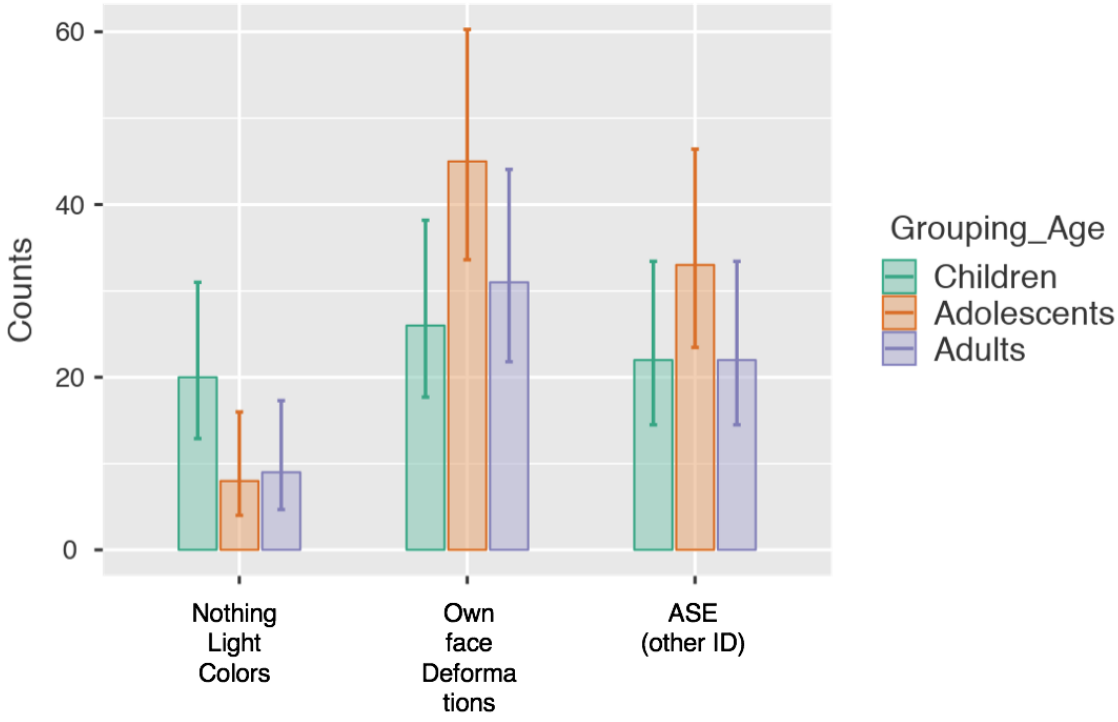


Figure 13: Comparison of the percentages of children adolescents and adults in the different MGT groups

3.3 Relationship between self-reported schizotypy dimensions and propensity to experience MGT-induced ASEs

Descriptive statistics of schizotypy dimensions by MGT groups are presented in Table 8.

Descriptive

	MGT Group	SPQ positive	SPQ negative	SPQ disorganized
Mean	Light/Color	4.14	5.43	3.22
	Own face deformation	7.03	6.71	4.30
	Other ID	7.38	6.78	4.90
Median	Light/Color	3	4	2
	Own face deformation	5.00	6.00	4.00
	Other ID	6	6	4
Standard deviation	Light/Color	4.06	4.23	3.18
	Own face deformation	6.52	5.32	3.70
	Other ID	5.82	4.41	3.23
Minimum	Light/Color	0	0	0
	Own face deformation	0	0	0
	Other ID	0	0	0
Maximum	Light/Color	16	18	14
	Own face deformation	29	23	14
	Other ID	31	20	13

Table 8: Descriptive statistics of schizotypy dimensions mean scores in the different MGT groups (1: light/colors, 2: own face deformations, 3: other identity).

When comparing self-reported schizotypy scores between the three MGT groups, we observed statistically significant differences for the positive (χ^2=10.7, p=0.005) and disorganized (χ^2=9.05, p=0.011) dimensions, but no difference for the negative schizotypal dimension (χ^2=2.62, p>0.05) (see Table 9). More precisely, pairwise comparisons showed differences

between the group light/color and the other identity group on the positive (W=5.03, *p*=0.001; see Table 4) and disorganized (W=4.55, *p*=0.004; see Table 4) dimensions; see Figure 14.

Kruskal-Wallis

	χ^2	df	p	ε^2
SPQ positive	10.70	2	0.005	0.498
SPQ negative	2.62	2	0.270	0.122
SPQ disorganized	9.05	2	0.011	0.421

Pairwise comparisons – SPQ positive

		W	p
Light/Colors	Own face deformation	3.19	0.063
Light/Colors	Other ID	5.03	0.001
Own face deformation	Other ID	1.42	0.574

Pairwise comparisons – SPQ negative

		W	p
Light/Colors	Own face deformation	1.494	0.541
Light/Colors	Other ID	2.508	0.179
Own face deformation	Other ID	0.795	0.840

Pairwise comparisons – SPQ disorganized

		W	p
Light/Colors	Own face deformation	2.05	0.315
Light/Colors	Other ID	4.55	0.004
Own face deformation	Other ID	2.36	0.217

Table 9: Statistical analyses of comparison of SPQ dimensions between MGT groups (light/color vs own face deformation vs other identity).

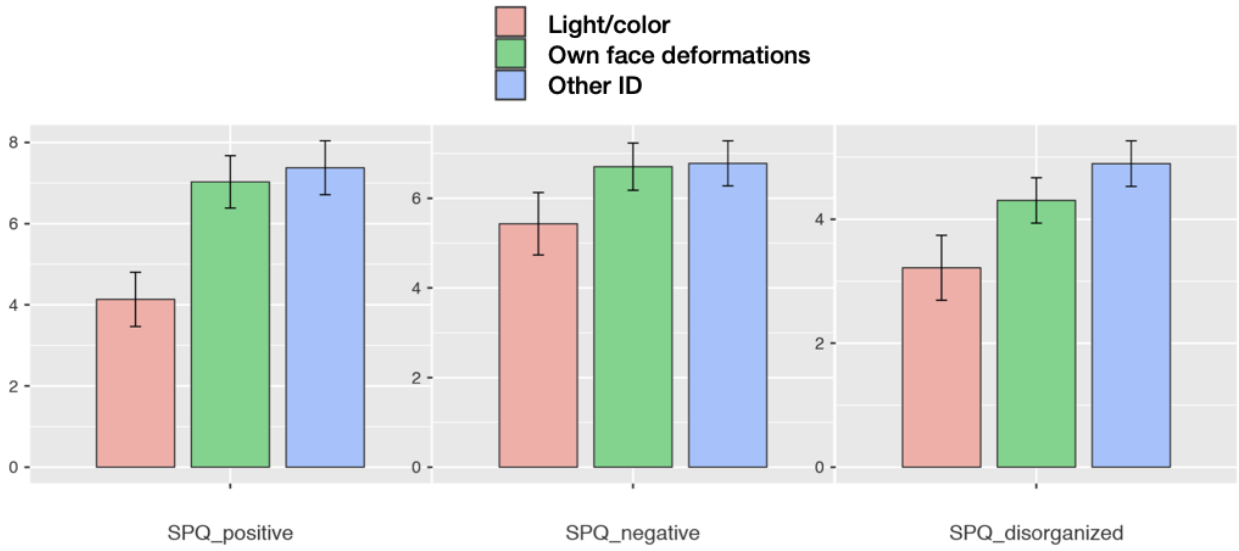


Figure 14: Comparison of SPQ dimensions between MGT groups

3.4 Developmental model of self-reported schizotypy and propensity to experience MGT-induced ASEs

Table 10 shows a descriptive analysis of age and schizotypy dimensions scores in the nine different possible combinations of age and MGT groups: 1 children–light/color, 2 adolescents–light/color, 3 adults–light/color, 4 children–own face deformation, 5 adolescents–own face deformation, 6 adults–own face deformation, 7 children–other identity, 8 adolescents–other identity, 9 adults–other identity.

The overall interaction effect between age group and MGT group was confirmed with log likelihood ratio tests for the three dimensions of schizotypy (positive: χ^2 =56.25, p<0.001; negative: χ^2 =53.6, p<0.001; disorganized: χ^2 =47.26, p<0.001); see Appendix 5.

	Group Age	Group MGT	SPQ positive	SPQ negative	SPQ disorganized
N	Children	Light/Colors	20	20	20
		Own face deformation	26	26	26
		Other ID	22	22	22
	Adolescents	Light/Colors	8	8	8
		Own face deformation	45	45	45
		Other ID	33	33	33
	Adults	Light/Colors	9	9	9
		Own face deformation	31	31	31
		Other ID	22	22	22
Mean	Children	Light/Colors	2.65	3.95	2.25
		Own face deformation	3.73	4.54	2.92
		Other ID	4.91	4.73	4.09
	Adolescents	Light/Colors	8.13	9.00	7.00
		Own face deformation	10.5	9.20	6.02
		Other ID	10.1	8.64	6.12
	Adults	Light/Colors	3.89	5.56	2.00
		Own face deformation	4.77	4.90	2.97
		Other ID	5.73	6.05	3.86
Range	Children	Light/Colors	0-7	1-8	0-6
		Own face deformation	0-8	1-9	0-6
		Other ID	1-8	1-8	0-6
	Adolescents	Light/Colors	3-16	3-18	1-14
		Own face deformation	2-24	2-17	1-12
		Other ID	4-25	2-17	1-13
	Adults	Light/Colors	0-13	0-11	0-5
		Own face deformation	0-29	0-23	0-14
		Other ID	0-31	0-20	0-13

Table 10: Descriptive statistics for analysis 4 based on MGT, schizotypy dimensions, and Age groups.

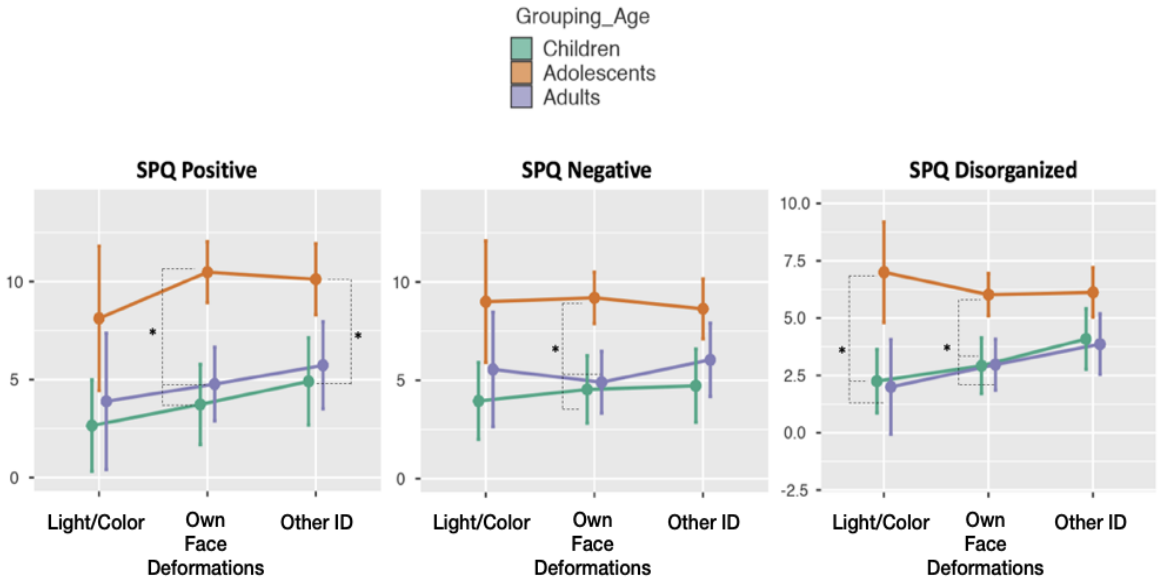


Figure 15: Comparison of self-reported schizotypy between group age x group MGT (The Y axis represents the values of estimated marginal means for each SPQ dimension, and interval confidence are represented on the means)

Positive Schizotypy

For positive schizotypy, when estimating the parameters inserted in the model, we observed that the interaction between MGT group and age group was statistically significant when the age group parameter was modelled as quadratic (light/color × age quadratic: Z=–2.24, p=0.026; own face deformation × age quadratic: Z=–5.87, p<0.001; other identity × age quadratic: Z=–3.92, p<0.001). See Appendix 5.

Post-hoc comparison showed statistically significant differences in self-reported positive schizotypy between children and adolescents who reported experiencing other identity (Z=–3.56, p=0.013), and between children and adolescents who reported deformations of their own face (Z=–5.15, p<0.001). Moreover, adolescents who reported deformations of their own face

scored higher on self-reported positive schizotypy than adults who reported the same type of illusions on the MGT (Z=4.6, p<0.001). See Table 11.

Post Hoc Comparisons - Group Age × Group MGT – Positive Schizotypy

Comparison								
Group Age	Group MGT		Group Age	Group MGT	Difference	SE	z	$p_{bonferroni}$
Children	Own face deformation	-	Adults	Own face deformation	-1.043	1.42	-0.737	1.000
Children	Own face deformation	-	Adolescents	Own face deformation	-6.758	1.31	-5.154	< .001
Children	Other ID	-	Adults	Other ID	-0.818	1.60	-0.509	1.000
Children	Other ID	-	Adolescents	Other ID	-5.212	1.46	-3.557	0.013
Children	Light/Colors	-	Adults	Light/Colors	-1.239	2.14	-0.579	1.000
Children	Light/Colors	-	Adolescents	Light/Colors	-5.475	2.23	-2.459	0.502
Adolescents	Own face deformation	-	Adults	Own face deformation	5.715	1.24	4.600	< .001
Adolescents	Other ID	-	Adults	Other ID	4.394	1.46	2.999	0.097
Adolescents	Light/Colors	-	Adults	Light/Colors	4.236	2.59	1.6380	1.000

Table 11: Statistical analysis for positive schizotypy

Negative Schizotypy

For negative schizotypy, when estimating the parameters inserted in the model, we observed that the interaction between MGT group and age group was statistically significant when the age group parameter was modelled as quadratic (light/color × age quadratic: Z=–2.34, p=0.020; own face deformation × age quadratic: Z=–5.03, p<0.001; other identity × age quadratic: Z=–3.16, p=0.002). See Appendix 5.

Looking at post-hoc comparisons, we observed that adolescents who reported deformations of their own face scored higher on self-reported negative schizotypy than children and adults who reported the same type of illusions on the MGT (Z=–4.24, p<0.001 and Z=4.13, p=0.001, respectively). See Table 12.

Post Hoc Comparisons - Group Age × Group MGT – Negative Schizotypy

Comparison					Difference	SE	z	$p_{bonferroni}$
Group Age	Group MGT		Group Age	Group MGT				
Children	Own face deformation	-	Adults	Own face deformation	-0.365	1.19	-0.308	1.000
Children	Own face deformation	-	Adolescents	Own face deformation	-4.662	1.10	-4.243	< .001
Children	Other ID	-	Adults	Other ID	-1.318	1.34	-0.980	1.000
Children	Other ID	-	Adolescents	Other ID	-3.909	1.23	-3.185	0.052
Children	Light/Colors	-	Adults	Light/Colors	-1.606	1.79	-0.897	1.000
Children	Light/Colors	-	Adolescents	Light/Colors	-5.050	1.87	-2.707	0.244
Adolescents	Own face deformation	-	Adults	Own face deformation	4.297	1.04	4.128	0.001
Adolescents	Other ID	-	Adults	Other ID	2.591	1.23	2.111	1.000
Adolescents	Light/Colors	-	Adults	Light/Colors	3.444	2.17	1.590	1.000

Table 12: Statistical analysis for negative schizotypy

Disorganized schizotypy

For disorganized schizotypy, when estimating the parameters inserted in the model, we observed that the interaction between MGT group and age group was statistically significant when the age group parameter was modelled as quadratic (light/color × age quadratic: Z=–3.80, p<0.001; own face deformation × age quadratic: Z=–4.88, p<0.001; other identity × age quadratic: Z=–2.95, p=0.004). See Appendix 5.

Post-hoc comparison showed statistically significant differences in self-reported disorganized schizotypy between children and adolescents experiencing own face deformations (Z=–3.98, p=0.002), as well as between children and adolescents who reported change in light/color (Z=–3.59, p<0.012). Moreover, adolescents who reported own face deformations scored higher on self-reported disorganized schizotypy than adults who reported experiencing the same type of illusions (Z=4.14, p<0.001). The same relationship was observed between adolescents and adults who reported seeing slight changes in light and/or color (Z=3.26, p=0.04). See Table 13.

Post Hoc Comparisons - Group Age × Group MGT – Disorganized Schizotypy

Comparison								
Group Age	Group MGT		Group Age	Group MGT	Difference	SE	z	$p_{bonferroni}$
Children	Own face deformation	-	Adults	Own face deformation	-0.0447	0.840	-0.0532	1.000
Children	Own face deformation	-	Adolescents	Own face deformation	-3.0991	0.778	-3.9827	0.002
Children	Other ID	-	Adults	Other ID	0.2273	0.952	0.2386	1.000
Children	Other ID	-	Adolescents	Other ID	-2.0303	0.869	-2.3352	0.703
Children	Light/Colors	-	Adults	Light/Colors	0.2500	1.268	0.1972	1.000
Children	Light/Colors	-	Adolescents	Light/Colors	-4.7500	1.321	-3.5946	0.012
Adolescents	Own face deformation	-	Adults	Own face deformation	3.0545	0.737	4.1428	0.001
Adolescents	Other ID	-	Adults	Other ID	2.2576	0.869	2.5966	0.339
Adolescents	Light/Colors	-	Adults	Light/Colors	5.0000	1.535	3.2575	0.040

Table 13: Statistical analysis for disorganized schizotypy

Discussion

The goal of the present study was to examine the developmental trajectory of proneness to strange face illusions from childhood to young adulthood and investigate the relationship with schizotypy personality traits. To our knowledge, this is the first study to examine non-clinical ASE-like states in children compared with adolescents and young adults in a non-enriched sample (i.e., not guided by level of concern for future psychosis) using an experimental task. First, our results substantiated the developmental trajectory of the SPQ dimensions, showing a peak during adolescence, while lower levels were observed during childhood and adulthood. Second, we confirmed the hypothesis that the developmental evolution of proneness to induced self-distortions followed the trajectory of schizotypy traits, with a peak during adolescence. Third, we found that positive and disorganized self-reported schizotypy appear to increase the proneness to strange-face illusions in the mirror. Finally, we tested a developmental model of

the relationship between proneness to different types of induced ASE phenomena and schizotypal personality traits from childhood to adulthood.

[Relative prevalence of strange face illusion and developmental considerations]

The results of the study showed, first, that other facial identity illusions are quite prevalent among typically developing individuals (36%) and are more frequently observed during adolescence. The prevalence of MGT-induced other identity in adolescents was 43%, while children and adults showed a prevalence of 29%. Confirming this result, in our previous study, typically developing adolescents showed a prevalence of this illusion of almost 40% (Derome et al., 2018). In Fonseca-Pedrero and colleagues' research (Fonseca-Pedrero, et al., 2015), the prevalence of other-identity was slightly lower in adolescents from the general population, with a reported prevalence of approximately 35%. No research linking the prevalence of ASEs to childhood development was available; our results suggest a proneness to experimentally induced other-identity during childhood equivalent to that in young adulthood. Thus, the developmental trajectory of proneness to induced ASEs seems to follow that of schizotypal personality traits, peaking during adolescence and being lower in childhood and adolescence. This finding provides original evidence that would need to be confirmed using prospective longitudinal studies.

[Overlap between strange face illusions and schizotypy personality traits]

Secondly, results of the present study showed higher expression of positive and disorganized schizotypy traits in participants who experienced other-identity ASE phenomena (other facial identity, either human or non-human) compared with those who perceived only changes of light, color, or contrast. These findings confirmed previous results collected in an independent

sample of typically developing adolescents showing that those who experienced other facial identity presented higher scores on the positive and disorganized dimensions of schizotypy (Derome et al., 2018; Fonseca-Pedrero et al., 2015). Our results lend weight to considering MGT-induced ASEs as phenomena that characterize the way schizotypy may have influence on the perceptual apparatus during development, and specifically in adolescence. When reviewing accounts from high-risk states models, Raballo et al. (Raballo et al., 2016) also found significant associations between the presence of trait ASEs, as assessed with the Examination of Anomalous Self-Experiences, and attenuated positive symptoms.

Altogether, in line with existing literature, results of the present study seem to confirm our hypothesis that positive and disorganized schizotypy increase the proneness to induced ASEs, and seem to corroborate the extended findings observed in clinical high-risk states, at least for the positive dimension (Værnes et al., 2019). The present results seem to indicate that schizotypy might confer a perceptive bias during adolescence. Thus, this period should be further examined, notably regarding the link with the development of schizotypal personality as well as with different factors contributing to the expression of schizotypy.

[Developmental model of strange face illusions and schizotypy personality]

We tested a developmental model exploring the relationship between age, different strange face illusions (ASE-like phenomena), and the expression of schizotypy traits. The most important finding was the significant difference in positive self-reported schizotypy between children and adolescents experiencing another identity during the MGT. More precisely, positive schizotypy differed between children and adolescent groups experiencing own face deformation or other identity. Negative schizotypy differed only between children and adolescent groups experiencing own face deformation. Disorganized schizotypy differed

between children and adolescent groups, and between adult and adolescent groups, when they experienced light/color changes and own face deformations during the MGT. The conceptualization of schizotypy has proposed a unifying construct that efficiently links a broad continuum of subclinical psychosis manifestations including, among others, schizotypal traits, attenuated positive symptoms, and psychotic-like experiences (Kwapil & Barrantes-Vidal, 2015). However, the relationship between schizotypy and psychotic-like experiences is probably not static, as psychotic-like experiences are by definition transitory states and tend to disappear over time, notably during adolescence (Debbané & Barrantes-Vidal, 2015; Linscott & van Os, 2013) . Building upon this model, considering MGT-induced ASEs as transient state phenomena, we could observe that positive schizotypy tends to be the dimension that associates most consistently with proneness to experiencing experimentally induced other-identity phenomena between childhood and adolescence. This first confirms the interest of studying positive schizotypy at an early age, and to better understand the transition from one developmental stage to the other, to assess how these phenomena potentially translate into increased risk for psychosis. We did not expect to observe differences between children and adults experiencing ASE phenomena, but we did expect changes between adolescence and adulthood. This lack of result could be explained by the age range we used; some authors would consider adolescence, defined in terms of maturational processes, to continue until 24–25 years of age (McDonagh et al., 2018), whereas we included this age range in young adulthood in our study. Future studies should include a comparison with an older age group to investigate the development of schizotypy and ASE phenomena.

Strengths and limitations of the study

An important strength of the present study is the recruited sample, with participants ranging in age from 7 to 28 years. Moreover, the non-enriched nature of our sample gives power to this study, limiting the confounding factors of mental illness comorbidities, medication, and disruptions in educational pathways. This further allowed us to understand the development of task-induced ASE-like illusions before the onset of psychosis, and to specifically analyze their links to schizotypy personality traits, outside psychopathological expression. This advantage is also a limitation, however: because our sample did not include a comparison group of help-seeking individuals, it is difficult to generalize our findings to the general population of adolescents who are at risk for schizophrenia spectrum disorders.

Conclusion and future directions

The present results provide the first evidence that ASE-like self-disturbances, similar to schizotypy, are more common during adolescence in comparison to childhood and young adulthood. Secondly, positive schizotypy appears to underlie proneness to experimentally induced strange-face illusions from childhood to adolescence. Finally, the study provides background evidence for further investigation of the developmental relationship between ASEs, prodromal symptoms, and risk for schizophrenia.

4. Study 4 – Activation patterns preceding and ongoing task-induced visual illusions using the fMRI Mirror Gazing Task

Abstract

Patients with schizophrenia and individuals at high risk state for psychotic disorders have reported experiences of face distortions when confronted to their own specular image in the mirror. Whilst the use of high-risk model is a fruitful contribution to the field of early psychosis, the use of experimental paradigms in these clinical sample is hardly feasible. We propose an alternative methodology inducing transient psychotic-like experiences in individuals with heightened schizotypal traits. The so-called mirror phenomenon can be assessed in the general population, by inducing strange-face illusions with the mirror gazing task (MGT). We adapted the MGT in fMRI, accordingly, the present study explores the activated brain regions during the different stages of illusions. Fifty typically developing young adults, participated in a single 10 minutes session of mirror gazing in magnetic resonance imaging (MRI), and we could capture illusion experiences in Twenty-five of them. Based on the response button pattern of psychosensory experiences that occurred during scanning, illusory phenomena were identified and divided into four stages: period without illusions ('off'), period with illusions ('ongoing'), period just before the illusion occurred ('emergence') and extinction of the illusion experiences ('fading'). Thus, statistical analyses compared the samples obtained: n= 137 samples for the 'ON' condition, 315 for the 'OFF' condition, and 499 for the 'emergence' condition. By contrasting pairs of conditions, we observed that ongoing periods are characterized by activations in occipital and frontal cortices, insula and ventral anterior cingulate gyrus, while the OFF periods seem to recruit regions of the Default Mode Network. The transition between emergence and maintenance of illusions, and the transition between resting state OFF periods

and the emergence of illusions respectively involved activation of the dorsal posterior cingulate, and activation of the dorsal anterior cingulate and insula. Following our findings, we propose a hypothetical model of the neural correlates sustaining the course of visual illusions.

1. Introduction

Illusions can be defined as a mismatch between the objective and perceived features of an object of the environment and occur frequently in typical visual processing. The proneness to visual illusions can be considered as a normal phenomenon, and although they do not have psychopathological significance per se, they might be helpful to understand and make inference about the mechanisms sustaining subjective perceptual experiences and might help characterizing the perceptual disturbances observed in psychosis (Guillermo Horga & Abi-Dargham, 2019).

Visual illusions reflect the constraints developed by our brains to support the adaptive formation of visual representations describing our external environment (Eagleman, 2001). Such constraints lure us into perceiving a stable perceptual world, while our receptors continuously process and signal motion (i.e. body movement, eyes saccades), thus our visual experiences are in essence visual illusions (Rogers, 2014). Initially, Gregory (Gregory, 1997) introduced the idea that perception requires assumption, or prediction, which when inappropriate, favors illusions. A more recent model of information processing proposed by Corlett (Corlett et al., 2011) and retained by other authors (Corlett et al., 2011; Fletcher & Frith, 2009; Notredame et al., 2014) suggests that experimental intervention that triggers forms of psychotic-like symptoms affect the interaction between the individual's predictions (endogenous priors) about the world and the sensory input (bottom-up sensory signal)

encountered. Thus, perceptions can be considered as projections of brain hypotheses that either match or not to a degree the physical reality.

One method to trigger illusions is sensory deprivation, following the predictive coding model, introducing a bias at the level of the sensory bottom-up input, can create the expected mismatch between prior's anticipation and incoming information. Caputo introduced a standardized experimental procedure that triggers visual illusions when gazing at one's own reflection in a mirror under specific sensory deprivation conditions - under very low illumination, the mirror gazing task (MGT) (Caputo, 2010) . In this context, one's own facial expressions are reflected in the mirror and subsequently, perceived and recognized by themselves (Caputo et al., 2014). Thus, this experimental set-up triggers illusions involving features of the self and could be related to the uncanny mirror phenomenon that is reported by some patients along the spectrum of psychotic disorders (Poletti & Raballo, 2019). These phenomena have been described by patients with schizophrenia and individuals at high risk state for psychotic disorders as experiences of face distortions when confronted to their own specular image in the mirror.

Concerning the neural correlates of hallucinatory phenomena, we can identity two types of functional neuroimaging studies, trait and state approaches. Trait studies usually compare hallucinators and non-hallucinators with regards to their brain activity while they rest in the scanner. Whilst in state studies, participants are scanned while experiencing a hallucinatory experience and indicate its onset and offset. A previously published trait-like study (Derome et al., 2018) showed atypical connectivity in adolescents seeing themselves as another identity during the MGT within the primary visual and default mode networks, involving areas implicated in the core steps of face-recognition stream. However, the MGT has never been performed in the scanner, thus this study would be the first to study non-clinical experimentally induced perceptual distortions in the specular image of one's self. This state study will include within subject designs and compare resting-state from illusory state.

In this study we are particularly interested in the period preceding the occurrence of a visual illusion, as in a few seconds equivalent to the brain's transition from a resting-state to the illusory experience. Adapted to a functional magnetic resonance imaging task (fMRI) we measure activations during illusions triggered by the 10 minutes MGT. Using a response button, we record the exact moment when participants experience an illusion, and we define emergence, ongoing and off periods of the course of illusions. The aim of the present study is to uncover the neural underpinnings preceding and ongoing visual illusions in order to understand their mechanisms of appearance during the fMRI-MGT. This study might provide a groundwork for the understanding of the mechanisms of emergence of visual hallucinations.

2. Methods

2.1 Participants

We recruited 50 French-speaking young adults (22 males, 28 females, mean age=22.5 Sd age=2.1) from the community with normal or corrected to normal vision. Due to the restriction of the task, 8 participants had to be excluded because they did not press the response-button (they did not perceive any change on the MGT) and 17 because they did not press for long enough to estimate activity (please refer to the next section for more details on the minimal press duration). The final sample included 25 participants (15 females, 10 males, mean age=22.7, Sd age=1.9). Young adults who experienced changes on the MGT represent 50% of our initial sample, which is in line with previous studies (Derome et al., 2018; Eduardo Fonseca-Pedrero, Badoud, et al., 2015). Participants received financial compensation, and written consent was obtained under protocols approved by the local ethical commission (Commission Centrale d'éthique de la Recherche des Hôpitaux Universitaires de Genève).

2.2 Experimental design and data acquisition

Young adults included in the study participated in a session of MRI acquisition on a 3T SIEMENS Trio scanner, which includes an anatomical sequence and a 10-minute fMRI-MGT sequence to experimentally induce illusions on one's specular image within the scanner. The 8 minutes anatomical T1-weighted sequence was acquired with the following parameters: TR=2500 ms, TE=3 ms, flip angle=8°, FOV=22cm, slice thickness=1.1 mm, 192 slices.

Regarding the fMRI task, we adapted a previously used behavioral task, the MGT (for the set-up of the task, see (Caputo, 2010d; Derome et al., 2018; Eduardo Fonseca-Pedrero, Badoud, et al., 2015)). For the fMRI Mirror Gazing Task (fMRI-MGT), we mounted a flat mirror on the antenna, so that participants could see their whole face (from forehead's hairline to the chin, but they could not see their hair or ears) while lying on the MRI bed. The mounted-mirror was placed 18 cm away from their eyes, due to restriction of space within the scanner. They were asked to lay still with their eyes open, to fix the convergence point on the top of the nose at equal distance of each eye, as well as to blink as little as possible. Activation during self-face mirror gazing was measured over 10 minutes, during which fMRI scans were made continuously. Participants were instructed to press a response button when they experienced changes while lying in the scanner and release it when the change disappeared. More precisely, they were asked to press different buttons depending on the content of their illusions: they were instructed to "press the first button and hold it down when you perceive a change in their faces" or "press the second button and hold it down if what you perceive is not your face". In addition, they were put in a dimly lit condition. To do so, light within the scanner was turned off and the scanner room was only lit with a light bulb on the ceiling at the level of patients' feet. The luminosity measured within the scanner at the level of the eyes was calibrated to 0.8 lux, which is in line with previous studies using the behavioral MGT: 0.8 lux corresponded to 0.2 $cd.m^{-2}$ in Caputo's study (Caputo, 2010d), and to the illumination provoked by a light bulb of 12V, 20W in other studies (Derome et al., 2018; Eduardo Fonseca-Pedrero, Badoud, et al., 2015).

In order to improve the power to detect significant activations, we applied a very fast scan sequence and employed a 3D Multi-Band Echo Planar Imaging sequence (mbepi). This was important as we intended to be as sensitive as possible for BOLD changes during the periods of ongoing illusions. The phenomenon of ongoing illusion that we wanted to investigate is challenging to study in an MR environment given that the timing of brief ongoing illusion periods cannot be predicted. Five hundred and eighty functional EPI volumes were acquired with the following parameters settings: TR=1000 ms, TE=30 ms, flip angle= 60^{o}, FOV=220 mm, slice thickness= 3.20 mm, slices= 40, TA :10 :02, PAT :2, Voxel size :1.8x1.8x3.2 mm.

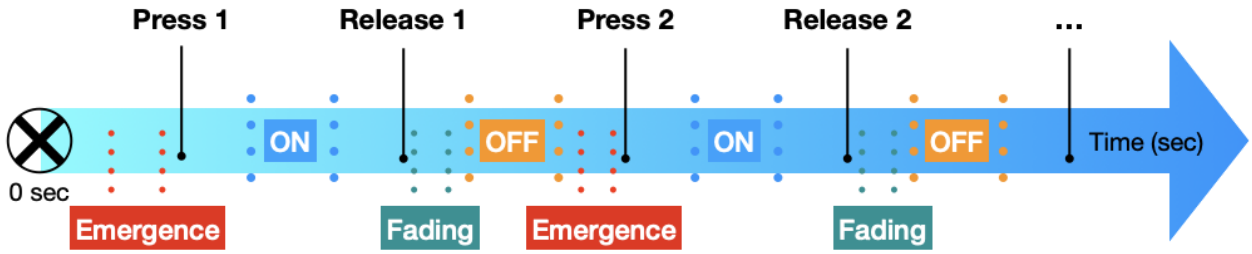
2.3 Data Analysis

Preprocessing

fMRI data were analyzed using statistical parametric mapping (SPM 12; Welcome Department of Cognitive Neurology, London, UK, https://www.fil.ion.ucl.ac.uk/spm/software/spm12/) implemented in Matlab_R2016b (https://ch.mathworks.com/). Preprocessing included firstly slice-timing correction and realignment. To control for motion-induced artifacts, head motion was estimated for each subject, excessive head motion (cumulative translation or rotation >1.5 mm or 1.5^{o}) was applied as an exclusion criterion. None of the participants included in the study were excluded for excessive head motion. Co-registration was performed using DARTEL (Diffeomorphic Anatomical Registration using Exponential Lie algebra) to create a population specific template. The resulting template was then spatially normalized to standard stereotaxic space (based on the Montreal Neurological Institute, MNI coordinate system). Following normalization, spatial smoothing was applied using an isotropic Gaussian smoothing Kernel with a full width at half maximum (FWHM) of 6mm in order to decrease spatial noise prior to statistical analysis.

Definition of the illusionary stages

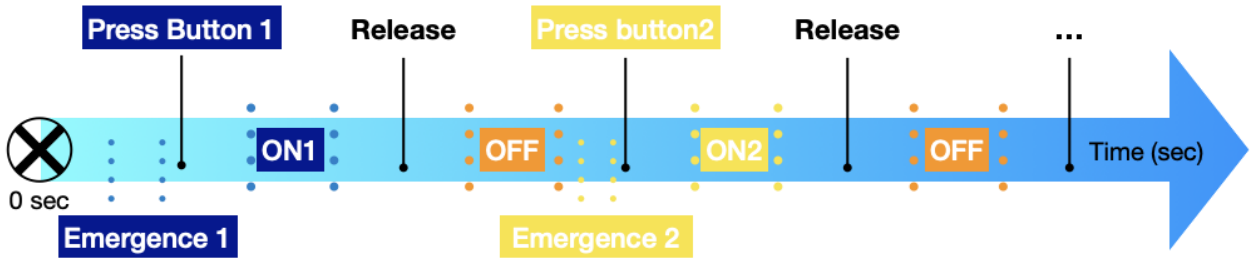
The definition of the illusionary stages was inspired by the methodology of Lefebvre and colleagues (Lefebvre et al., 2016), but readapted to our button-press acquisition. To define illusions experiences we used the response button press and release time periods as recorded by Eprime and translated in onsets and durations. Period minimal length was set at 3 seconds (3 consecutive EPI volumes), and periods below 3 seconds were discarded. The 3 seconds represented an arbitrary choice that we calculated on the whole original sample (n=50); we computed the average pressing time of our participants, which was of 2.8 seconds. Of note, whenever participants experience an illusion on the task, the episode is brief (only a few seconds). Therefore, we used 3 seconds (3 EPI volumes) as the minimum of consecutive volumes sufficient to estimate activity.



The 'ON' period was defined as at least more than 3 consecutive volumes between a button-press and a button-release (i.e. between *press 1* and *release 1*). The 'OFF' period corresponded to the time after the button-release and before the next button-press (i.e. between *release 1* and *press 2*). An additional step was conducted to ensure pure 'ON' and 'OFF' activation (i.e. we wanted to make sure that the BOLD signal corresponding to the ON or OFF period did not merge with emergence or fading ones). Therefore, we removed the first 3 volumes after the button-press (i.e. 3 volumes after *press 1*) and the three last volumes before the button-release (i.e. 3 volumes before *release 1*) for the 'ON'. For the 'OFF' condition, we removed the three

volumes after the release (i.e. 3 volumes after *release 1*) and 3 volumes before the next press (i.e. 3 volumes before *press 2*).

The emergence period was defined as 3 seconds before a button-press, and the fading stage corresponded to three seconds after a button-release. Thus, the duration of ON and OFF periods could vary depending of the time participants held the button down, but emergence and fading periods were always defined by a stable duration of 3 seconds. Each participant had more than one illusion during the 10 minutes of the MGT, therefore we had more sample than participants, and samples were used to define the different conditions. In the end, we obtained n= 137 samples for the 'ON' condition, 315 for the 'OFF' condition, 499 for the 'emergence', and n=600 for the 'fading' condition. Therefore, instead of statistically comparing groups of subjects, we compared conditions (i.e. when comparing the 'ON' and 'OFF' condition, we actually compared two groups composed of n=137 ON versus n=315 OFF).



In a second time, we performed post-hoc analyses that took into account the content of illusionary phenomena, thus we computed different ongoing and emerging conditions depending on whether participants pressed the first button (when they perceived a change on their faces) or the second one (if they perceived something else than their faces). Thus, we could compare the emergence and ongoing periods of a 'perceptual change' versus an 'identity change'. Using the same methodology as above, we identified 'emergence 1' and 'ON1' periods corresponding to the emergence and ongoing perceptual change; and 'emergence 2'

and ‘ON2’ periods characterizing the emergence and ongoing of an identity change. ‘ON1’ consisted of n=102 samples, ‘ON2’ of n=35; ‘emergence 1’ of n=325’ and ‘emergence 2’ of n=174’ samples.

Statistical MRI analyses

After preprocessing, the brain responses of each subject were estimated at every voxel using a general linear model. We first performed a one-sample t-test at the subject level to characterize activations related to the three conditions within subjects, namely: ‘ON’, ‘OFF’, ‘emergence’ and ‘fading’ using the onset and durations determined earlier. Age, sex, externalized and internalized behaviors were entered as covariates at the first level in each analysis without significant effects on the results obtained. Then, using two sample t-tests, we compared the different pairs of conditions; ‘emergence’ VS ‘ON’ samples, ‘ON’ VS ‘OFF’ samples, ‘emergence’ VS ‘OFF’ samples and ‘OFF’ VS ‘fading’ samples. S{T} maps were obtained with a threshold of $p<0.001$ and an extended threshold k of 50 voxels. Cluster level peak functional activity at $p<0.01$ (Family wise corrected) was then localized on a mean structural scan with Broadman areas estimated from the Talairach and Tournoux atlas (Talairach, J, 1998) after having converted coordinates from MNI to Talairach templates (http://www.talairach.org/about.html).

Regarding the post-hoc analyses investigating the differences between emergence and ongoing of perceptual VS identity change, we used the same methodology. However, results were presented uncorrected at the cluster level for a threshold of $p<0.05$, reflecting a tendency.

3. Results

3.1 Descriptive statistics of the 25 participants included in the study

The descriptive statistics of the 25 young adults indicated a mean age of 22,7 (sd= 1,87) ranging from 17,6 to 25,2 years old. The sample encompassed 15 females and 10 males. The mean score on the externalized dimension was 54 (sd= 8,59) with a minimum of 34 and a maximum of 74. Finally, the mean score on the internalized dimension was 55,4 (sd= 6,72) ranging from 42 to 68. The following types of visual illusions were observed in our sample: 40% (n=10) experienced deformations of their own faces, 48% (n=12) reported seeing another human facial identity (other person, either known or unknown) and 12% (n=3) reported seeing a non-human identity (monsters, animals). In the following first analyses we did not take into account the content of illusion that participants experienced. Any of these four types of experiences were considered as illusions (ON vs OFF, ON vs emergence, OFF vs emergence and OFF vs fading).

Post-hoc analyses were conducted on perceptual vs identity change: perceptual changes included deformation of one's own face, whereas identity changes included other identity vision (either human or non-human).

3.2 ON vs OFF

When contrasting the ON and the OFF periods significant differences were observed for both contrasts: ON>OFF and OFF>ON.

The ongoing period (ON) was characterized by higher activations in right superior frontal gyrus (Brodmann area 10: t=8.86, p-fwecorr<0.000; BA 6: t=5.93, p-fwecorr<0.000) and left precentral gyrus (t=7,69, p-fwecorr<0,000). In the occipital lobe (left middle occipital gyrus: t=8,24, p-fwecorr<0.000; right fusiform gyrus BA 19: t=5,17, p-fwecorr<0.000). In the Temporal lobe (left middle temporal gyrus: t=6.49, p-fwecorr<0,000; right fusiform gyrus BA 37: t=5,81, p-fwecorr<0,000). In the parietal lobe (right inferior parietal lobule: t=6,67, p-fwecorr<0,000; right postcentral gyrus: t=5,87, p-fwecorr<0,000). In the right ventral anterior

cingulate gyrus (t=6,43, p-fwecorr<0,000) and in bilateral anterior insula (right: t=7,52, p-fwecorr<0,000; left: t=6,68, p-fwecorr<0,000). *See figure 16 and table 14.*

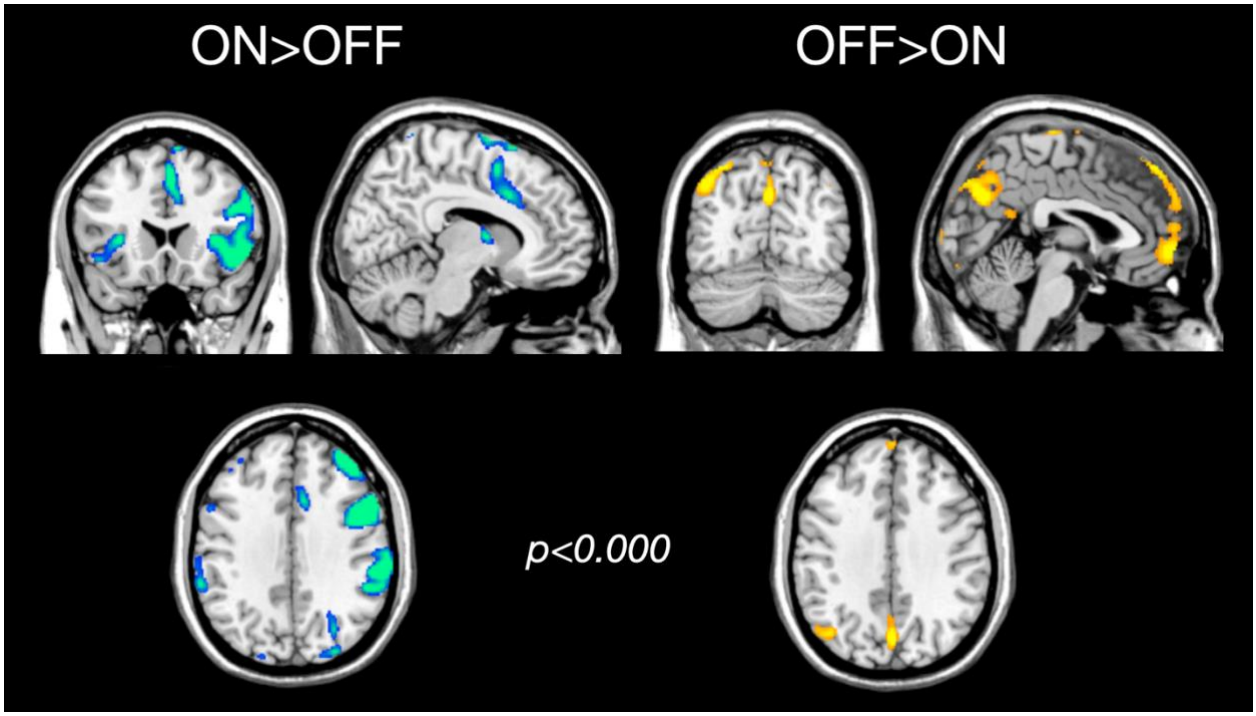


Figure 16: ON vs OFF

The OFF period of the course of illusions showed higher activations when compared to ON periods in the following regions: in the bilateral medial frontal gyrus (right: t=5,30, p-fwecorr<0,000; left: t=4,75, p-fwecorr<0,000), in the temporal lobe (right fusiform gyrus: t=4,51, p-fwecorr<0,000; right middle: t=4,80, p-fwecorr<0,000 and inferior: t=4,15, p-fwecorr<0,000 temporal gyrus, and left middle temporal gyrus: t=4,80, p-fwecorr<0,000). The parietal lobe also showed greater activation in the left angular gyrus: t=5,40, p<0,000, and bilateral precuneus: left: t=4,53, p-fwecorr<0,000; left: t=4,25, p-fwecorr<0,000). Finally, higher activation was found in the parahippocampal gyrus bilaterally (left: t=4,78, p-

fwecorr<0,000; right: t=4,22, p-fwecorr<0,000) and the left dorsal posterior cingulate gyrus (t=4,68, p-fwecorr<0,000). See *table 14, figure 16.*

ON>OFF

Hemisphere	Lobe	Region	Brodmann Areas	cluster p(FWE-corr)	cluster p(FDR-corr)	cluster equivk	cluster p(unc)	x,y,z {mm}	peak T	peak equivZ
Right	**Frontal**	**Superior Frontal Gyrus**	**area 10**	**0.000**	**0.000**	**8657**	**0.000**	**36 54 22**	**8.86**	**5.06**
Right	**Sub-lobar**	**Insula**	**area 13**					**42 8 0**	**7.52**	**4.69**
Left	**Occipital**	**Middle Occipital Gyrus**	**area 18**	**0.000**	**0.000**	**1764**	**0.000**	**-40 -88 2**	**8.24**	**4.90**
Left	**Occipital**	**Middle Occipital Gyrus**	**area 19**					**-30 -76 20**	**6.51**	**4.35**
Left	**Temporal**	**Middle Temporal Gyrus**	**area 37**					**-44 -63 -2**	**6.49**	**4.34**
Left	Frontal	Precentral Gyrus	area 6	0.085	0.015	145	0.002	-44 -4 56	8.14	4.87
Left	**Frontal**	**Precentral Gyrus**	**area 44**	**0.000**	**0.000**	**1246**	**0.000**	**-50 9 6**	**7.69**	**4.74**
Left	**Sub-lobar**	**Insula**	**area 13**					**-28 22 10**	**6.68**	**4.41**
Left	**Sub-lobar**	**Insula**	**area 13**					**-42 4 0**	**6.21**	**4.23**
Right	**Parietal**	**Inferior Parietal Lobule**	**area 40**	**0.000**	**0.000**	**3111**	**0.000**	**57 -34 40**	**6.67**	**4.40**
Right	**Parietal**	**Inferior Parietal Lobule**	**area 40**					**51 -40 42**	**5.94**	**4.13**
Right	**Parietal**	**Postcentral Gyrus**	**area 2**					**62 -20 27**	**5.87**	**4.10**
Right	**Limbic**	**Cingulate Gyrus**	**area 24**	**0.000**	**0.000**	**1108**	**0.000**	**12 8 34**	**6.43**	**4.32**
Right	**Frontal**	**Superior Frontal Gyrus**	**area 6**					**9 10 56**	**5.93**	**4.13**
Right	**Limbic**	**Cingulate Gyrus**	**area 24**					**8 6 46**	**5.79**	**4.07**
Left	Parietal	Precuneus	area 7	0.344	0.062	93	0.011	-24 -45 45	6.28	4.26
Left	Parietal	Precuneus	area 7	0.037	0.008	177	0.001	-20 -58 38	6.07	4.18
Left	Sub-lobar	Lentiform Nucleus	Putamen	0.007	0.002	244	0.000	-16 8 4	5.82	4.08
Left	Sub-lobar	Lentiform Nucleus	Putamen					-22 0 4	5.60	3.99
Right	**Temporal**	**Fusiform Gyrus**	**area 37**	**0.000**	**0.000**	**739**	**0.000**	**39 -57 -6**	**5.81**	**4.08**
Right	**Temporal**	**Fusiform Gyrus**	**area 37**					**39 -48 -14**	**5.61**	**4.00**
Right	**Occipital**	**Fusiform Gyrus**	**area 19**					**33 -63 -4**	**5.17**	**3.81**
Left	Frontal	Precentral Gyrus	area 6	0.845	0.224	51	0.049	-34 4 24	5.48	3.94
Right	Frontal	Superior Frontal Gyrus	area 6	0.008	0.002	238	0.000	20 8 69	5.24	3.83
Right	Frontal	Superior Frontal Gyrus	area 6					9 2 70	4.63	3.55
Right	Frontal	Sub-Gyral	area 6					22 4 58	4.06	3.25
Left	Parietal	Postcentral Gyrus	area 40	0.575	0.109	72	0.022	-60 -18 21	4.90	3.68
Right	Parietal	Postcentral Gyrus	area 40	0.501	0.095	78	0.018	54 -30 52	4.76	3.61
Right	Occipital	Middle Occipital Gyrus	area 19	0.294	0.055	99	0.009	38 -84 12	4.44	3.45

OFF>ON

Hemisphere	Lobe	Region	Brodmann	cluster p(FWE-corr)	cluster p(FDR-corr)	cluster equivk	cluster p(unc)	x, y, z (mm)	peak T	Peak equivZ
Left	**Parietal**	**Angular Gyrus**	**area 39**	**0.000**	**0.000**	**1006**	**0.000**	**-46 -69 33**	**5.40**	**10.29**
Left	**Parietal**	**Precuneus**	**area 19**					**-44 -75 39**	**4.53**	**7.03**
Left	**Parietal**	**Precuneus**	**area 19**					**-33 -75 42**	**3.50**	**4.54**
Left	Limbic	Parahippocampal Gyrus	area 28	0.001	0.000	350	0.000	-15 -20 -24	5.33	9.96
Right	**Frontal**	**Medial Frontal Gyrus**	**area 10**	**0.000**	**0.000**	**3633**	**0.000**	**4 57 -2**	**5.30**	**9.85**
Left	**Frontal**	**Medial Frontal Gyrus**	**area 11**					**-8 50 -9**	**4.75**	**7.73**
Right	**Limbic**	**Parahippocampal Gyrus**	**area 35**	**0.000**	**0.000**	**590**	**0.000**	**20 -26 -12**	**5.12**	**9.07**
Right	**Temporal**	**Fusiform Gyrus**	**area 20**					**39 -4 -22**	**4.51**	**6.99**
Right	**Limbic**	**Parahippocampal Gyrus**	**area 35**					**26 -22 -21**	**4.22**	**6.18**
Left	Temporal	Superior Temporal Gyrus	area 38	0.279	0.036	101	0.009	-38 8 -24	5.00	8.62
Left	Frontal	Medial Frontal Gyrus	area 8	0.000	0.000	1755	0.000	-3 50 45	4.94	8.38
Left	Frontal	Superior Frontal Gyrus	area 8					-22 16 44	4.53	7.03
Left	Frontal	Superior Frontal Gyrus	area 8					-8 52 39	4.28	6.32
Left	**Temporal**	**Middle Temporal Gyrus**	**area 21**	**0.000**	**0.000**	**805**	**0.000**	**-51 -14 -18**	**4.80**	**7.91**
Left	**Temporal**	**Middle Temporal Gyrus**	**area 21**					**-60 0 -16**	**4.22**	**6.18**
Left	**Temporal**	**Inferior Temporal Gyrus**	**area 20**					**-63 -21 -18**	**4.15**	**5.98**
Left	Frontal	Precentral Gyrus	area 4	0.006	0.001			-12 -30 66	4.58	7.19
Left	Frontal	Medial Frontal Gyrus	area 6					-9 -24 60	3.19	3.96
Left	**Limbic**	**Parahippocampal Gyrus**	**area 30**	**0.000**	**0.000**	**2439**	**0.000**	**-8 -36 4**	**4.78**	**7.82**
Left	**Limbic**	**Posterior Cingulate**	**area 31**					**-4 -54 24**	**4.68**	**7.50**
Right	**Parietal**	**Precuneus**	**area 7**					**3 -57 30**	**4.25**	**6.25**
Left	Occipital	Cuneus	area 18	0.158	0.022	122	0.005	0 -99 4	4.73	7.66
Right	Occipital	Cuneus	area 18					4 -99 12	3.51	4.57
Right	Occipital	Lingual Gyrus	area 18	0.002	0.000			6 -90 -14	4.46	6.82
Right	Temporal	Superior Temporal Gyrus	area 38	0.124	0.018	131	0.003	42 20 -39	4.39	6.63
Left	Parietal	Postcentral Gyrus	area 7	0.029	0.005	186	0.001	-3 -48 72	4.35	6.52
Left	Parietal	Postcentral Gyrus	area 5					-8 -45 63	3.61	4.76
Right	**Temporal**	**Middle Temporal Gyrus**	**area 21**	**0.000**	**0.000**	**591**	**0.000**	**56 -4 -18**	**4.26**	**6.28**
Right	**Temporal**	**Middle Temporal Gyrus**	**area 21**					**66 -14 -8**	**4.04**	**5.72**
Right	**Temporal**	**Middle Temporal Gyrus**	**area 21**					**63 -2 -15**	**4.02**	**5.67**
Right	Limbic	Posterior Cingulate	area 30	0.279	0.036	101	0.009	8 -51 10	4.24	6.22
Right	Frontal	Middle Frontal Gyrus	area 8	0.055	0.009	162	0.001	26 28 40	4.21	6.14
Right	Frontal	Middle Frontal Gyrus	area 8					27 40 48	3.20	3.97
Left	Limbic	Parahippocampal Gyrus	area 36	0.006	0.001			-27 -39 -10	4.07	5.79
Right	Frontal	Superior Frontal Gyrus	area 10	0.772	0.142	57	0.039	18 58 9	4.08	5.81
Right	Frontal	Superior Frontal Gyrus	area 10					12 66 10	3.76	5.08
Left	Temporal	Middle Temporal Gyrus	area 21	0.512	0.075	77	0.019	-48 10 -36	4.07	5.79
Left	Frontal	Paracentral Lobule	area 6	0.019	0.004	204	0.000	-3 -28 60	3.89	5.36
Right	Frontal	Paracentral Lobule	area 6					4 -30 56	3.67	4.88
Right	Parietal	Paracentral Lobule	area 4					4 -36 63	3.46	4.46
Right	Parietal	Angular Gyrus	area 39	0.225	0.031	109	0.007	54 -66 36	3.78	5.11
Right	Temporal	Superior Temporal Gyrus	area 39					57 -64 28	3.26	4.09
Left	Parietal	Superior Parietal Lobule	area 7	0.109	0.017	136	0.003	-2 -70 57	3.59	4.72
Left	Parietal	Precuneus	area 7					-2 -52 56	3.54	4.62
Left	Parietal	Precuneus	area 7					-2 -60 58	3.17	3.92

Table 14: results of the analysis ON versus OFF periods. Upper part: ON>OFF, lower part: OFF>ON

3.3 ON vs Emergence

When contrasting the ongoing period and the period emergence of illusions, significant differences in activations were found for both contrasts: ON>Emergence and Emergence>ON.

The ON period was characterized by higher activation in the right dorsal posterior cingulate (t=7,32, p-fwecorr<0,000) and right ventral posterior cingulate (t=5,76, p-fwecorr<0,000) gyri. *See table 15 and figure 17.*

During the emergence period activations were significantly higher in the frontal lobe (left: t=6,86, p-fwecorr<0,000 and right :t=5,16, p-fwecorr<0.000 superior frontal gyri and left medial frontal gyrus: t=4,65, p-fwecorr<0,000) and in the parietal lobe (left postcentral gyrus:

t=7,69, p<0,000; left inferior parietal lobule: t=6,58, p-fwecorr<0.000). *See table 15 and figure 17.*

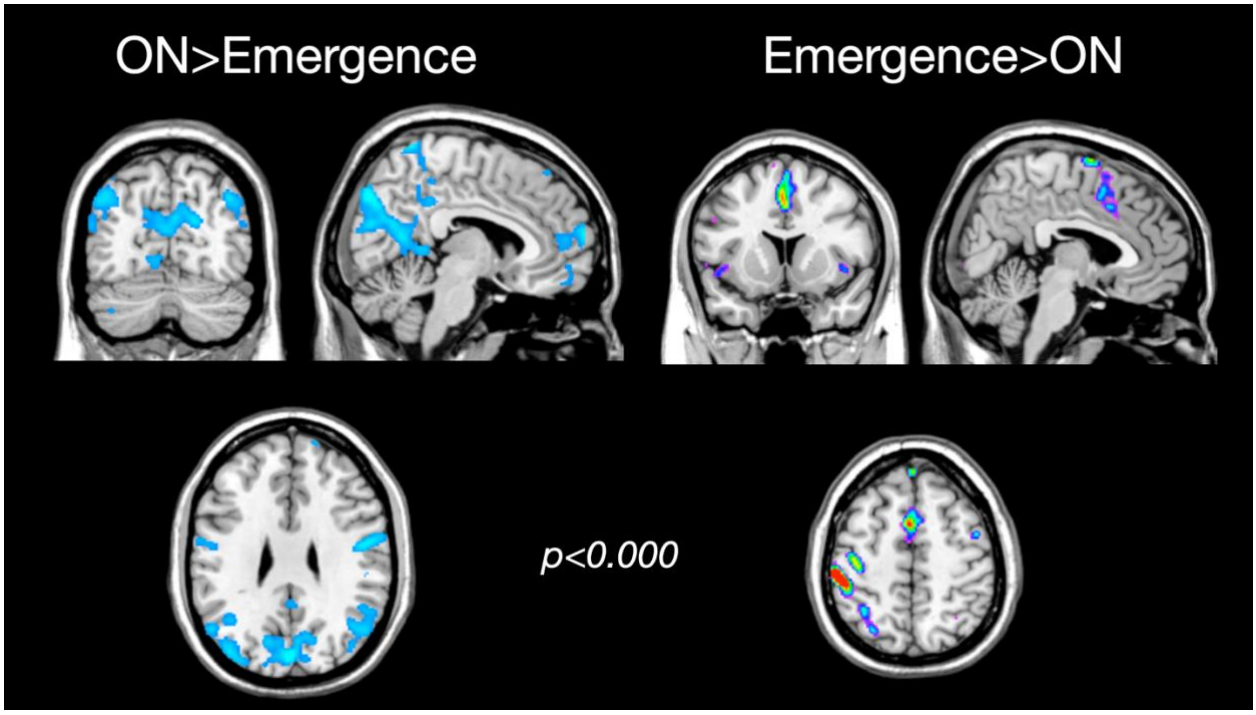


Figure 17: ON vs Emergence

ON>EMERGENCE

Hemisphere	Lobe	Region	Brodmann Areas	cluster p(FWE-corr)	cluster p(FDR-corr)	cluster equivk	cluster p(unc)	x,y,z {mm}	peak T	peak equivZ
Left	Occipital	Superior Occipital Gyrus	area 19	0.003	0.001	285	0.000	-40 -81 30	9.23	5.16
Left	Occipital	Superior Occipital Gyrus	area 19					-34 -86 33	8.18	4.88
Left	Temporal	Angular Gyrus	area 39					-48 -75 33	6.61	4.38
Right	**Limbic**	**Posterior Cingulate**	**area 31**	**0.000**	**0.000**	**522**	**0.000**	**22 -62 16**	**7.32**	**4.62**
Right	**Limbic**	**Posterior Cingulate**	**area 23**					**10 -54 16**	**5.76**	**4.06**
Left	Occipital	Lingual Gyrus	area 19	0.069	0.015	156	0.002	-8 -64 0	6.71	4.42
Right	Parietal	Precuneus	area 19	0.001	0.000	372	0.000	42 -72 33	6.61	4.38
Right	Temporal	Middle Temporal Gyrus	area 39					46 -63 30	6.33	4.28
Right	Temporal	Middle Temporal Gyrus	area 39					51 -63 21	4.97	3.71
Left	Limbic	Posterior Cingulate	area 30	0.001	0.000	367	0.000	-12 -54 10	6.61	4.38
Left	Limbic	Posterior Cingulate	area 31					-18 -58 20	5.51	3.96
Left	Limbic	Posterior Cingulate	area 29					-4 -57 12	4.65	3.56
Right	Frontal	Precentral Gyrus	area 6	0.564	0.131	74	0.022	42 -8 33	6.58	4.37
Right	Temporal	Middle Temporal Gyrus	area 21	0.152	0.029	126	0.004	62 -4 -22	5.79	4.07
Left	Occipital	Precuneus	area 31	0.807	0.234	55	0.044	-16 -72 26	5.63	4.00
Left	Occipital	Cuneus	area 19	0.013	0.004	225	0.000	-9 -82 30	5.63	4.00
Left	Occipital	Cuneus	area 18					-6 -82 16	4.34	3.40
Left	Parietal	Precuneus	area 19					-16 -84 42	4.13	3.29
Right	Temporal	Superior Temporal Gyrus	area 22	0.073	0.015	154	0.002	66 -20 4	5.19	3.81
Right	Temporal	Superior Temporal Gyrus	area 42					60 -24 10	4.36	3.41
Right	Temporal	Superior Temporal Gyrus	area 41					52 -21 8	4.33	3.39

EMERGENCE>ON

Hemisphere	Lobe	Region	Brodmann Areas	cluster p(FWE-corr)	cluster p(FDR-corr)	cluster equivk	cluster p(unc)	x,y,z {mm}	peak T	peak equivZ
Left	Frontal	Superior Frontal Gyrus	area 6	0.169	0.050	122	0.005	-10 9 70	8.46	4.96
Left	Parietal	Postcentral Gyrus	area 43	0.002	0.001	319	0.000	-51 -18 16	8.17	4.88
Left	Parietal	Postcentral Gyrus	area 2					-60 -21 28	4.58	3.52
Left	**Parietal**	**Postcentral Gyrus**	**area 2**	**0.000**	**0.000**	**1195**	**0.000**	**-48 -24 44**	**7.69**	**4.74**
Left	**Parietal**	**Inferior Parietal Lobule**	**area 40**					**-45 -34 56**	**6.58**	**4.37**
Left	**Parietal**	**Inferior Parietal Lobule**	**area 40**					**-39 -28 42**	**5.25**	**3.84**
Left	**Frontal**	**Superior Frontal Gyrus**	**area 8**	**0.000**	**0.000**	**670**	**0.000**	**-4 15 51**	**6.86**	**4.47**
Right	**Frontal**	**Superior Frontal Gyrus**	**area 8**					**8 15 51**	**5.16**	**3.80**
Left	**Frontal**	**Medial Frontal Gyrus**	**area 6**					**-2 4 60**	**4.65**	**3.56**
Left	Limbic	Ant Cingulate Gyrus	area 32	0.030	0.010	189	0.001	-10 21 32	6.23	4.24
Left	Limbic	Ant Cingulate Gyrus	area 32					-9 32 26	4.26	3.36
Right	Parietal	Inferior Parietal Lobule	area 40	0.308	0.082	99	0.010	39 -39 39	5.38	3.90
Right	Parietal	Precuneus	area 7					28 -46 39	4.02	3.22
Left	Frontal	Middle Frontal Gyrus	area 9	0.864	0.382	50	0.053	-50 28 30	4.66	3.56

Table 15: Results of the analysis ON vs Emergence, upper part: ON>Emergence, lower part: Emergence < ON

3.4 Emergence vs OFF

When contrasting emergence and OFF periods, significant differences in brain activation were only observed for the contrast emergence>OFF.

Activations were significantly higher during emergence periods when compared to OFF in the right superior (t=6,79, p-fwecorr<0,000) and left medial (t=5,01, p-fwecorr<0,000) frontal gyri; in the right dorsal anterior cingulate gyrus (t=4,69, p-fwecorr<0,000) and in the right anterior insula (t=8,08, p<0,000). *See table 16, figure 18.*

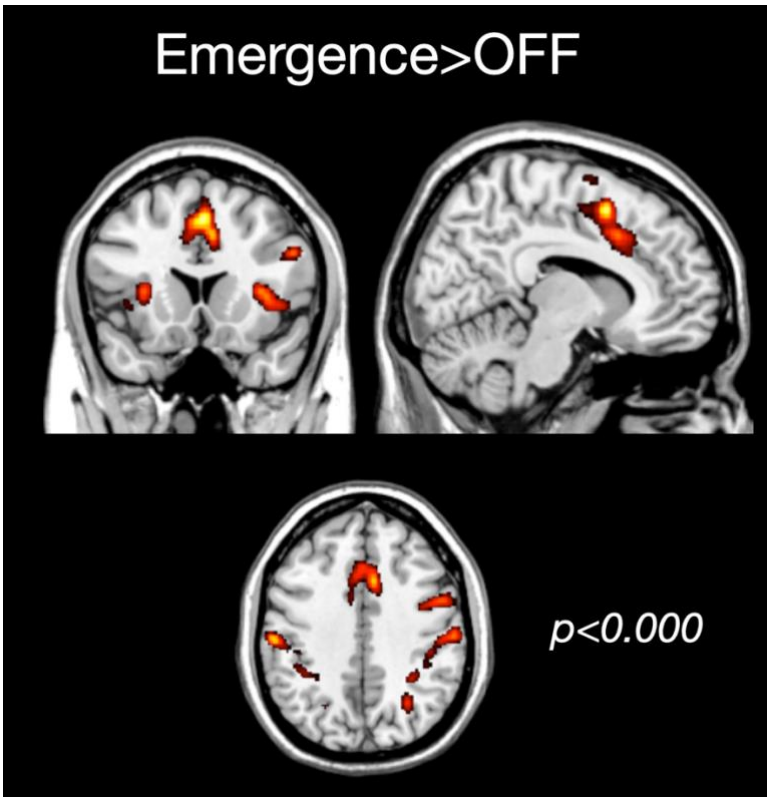


Figure 18: Emergence > OFF

Hemisphere	Lobe	Region	Brodmann Areas	cluster p(FWE-corr)	cluster p(FDR-corr)	cluster equivk	cluster p(unc)	x,y,z {mm}	peak T	peak equivZ
Right	**Sub-lobar**	**Insula**	**area 13**	**0.000**	**0.000**	**547**	**0.000**	**42 12 3**	**8.08**	**4.85**
Right	**Sub-lobar**	**Insula**	**area 13**					**34 20 0**	**6.24**	**4.25**
Right	**Sub-lobar**	**Insula**	**area 13**					**34 16 9**	**5.34**	**3.88**
Right	**Frontal**	**Superior Frontal Gyrus**	**area 6**	**0.000**	**0.000**	**674**	**0.000**	**10 12 51**	**6.79**	**4.45**
Left	**Frontal**	**Medial Frontal Gyrus**	**area 6**					**-3 14 46**	**5.01**	**3.73**
Right	**Limbic**	**Dorsal Anterior Cingulate Gyrus**	**area 32**					**9 15 40**	**4.69**	**3.58**
Right	Sub-lobar	Lentiform Nucleus	Putamen	0.750	0.121	65	0.043	20 9 6	6.30	4.27
Right	Frontal	Middle Frontal Gyrus	area 46	0.412	0.051	97	0.017	51 38 18	6.24	4.25
Left	Parietal	Inferior Parietal Lobule	area 40	0.021	0.005	232	0.001	-48 -36 46	5.38	3.90
Left	Parietal	Postcentral Gyrus	area 40					-40 -30 51	4.66	3.56
Left	Parietal	Inferior Parietal Lobule	area 40					-40 -32 42	4.15	3.30
Right	Parietal	Inferior Parietal Lobule	area 40	0.058	0.009	184	0.002	44 -32 42	5.21	3.82
Right	Parietal	Inferior Parietal Lobule	area 40					51 -27 44	5.01	3.73
Left	Parietal	Postcentral Gyrus	area 3	0.247	0.035	120	0.009	-44 -21 64	5.09	3.77
Left	Parietal	Postcentral Gyrus	area 1					-45 -30 66	4.42	3.44
Left	Parietal	Postcentral Gyrus	area 1					-51 -21 58	4.40	3.43
Right	Frontal	Inferior Frontal Gyrus	area 9	0.052	0.009	189	0.002	45 8 27	4.90	3.68
Right	Frontal	Precentral Gyrus	area 6					51 2 34	4.88	3.67
Left	Frontal	Precentral Gyrus	area 6	0.317	0.042	109	0.012	-38 3 27	4.71	3.59

Table 16: Results of the analysis Emergence vs OFF. Results were significant only when contrasting Emergence> OFF.

3.5 OFF vs Fading

No significant results were found when contrasting OFF and fading periods.

3.6 Post-hoc analysis: Perceptual vs identity change

No significant results were found when contrasting periods of ongoing perceptual change (ON1) and ongoing identity change (ON2).

However, for the analysis of emergence of perceptual (emergence 1) vs emergence of identity change (emergence 2), we found significant differences for the contrast emergence 1 > emergence 2. The emergence of perceptual change seemed sustained by activations in the right

superior frontal gyrus (t=5,37, punc<0,05), right dorsal anterior cingulate (t=5,24, punc<0,05), right inferior frontal gyrus (t=4,49, punc<0,05), the anterior insula (t=4,37, punc<0,05) and in the caudate (t=5,24, punc<0,05).

Emergence 1 > Emergence 2

Hemisphere	Lobe	Region	Brodmann Areas	cluster p(FWE-corr)	cluster p(FDR-corr)	cluster equivk	cluster p(unc)	x,y,z {mm}	peak T	peak equivZ
Right	**Frontal**	**Superior Frontal Gyrus**	**area 6**	**0.096**	**0.165**	**177**	**0.003**	**12 32 58**	**5.37**	**4.28**
Right	**Sub-lobar**	**Caudate**	**Caudate Body**	**0.635**	**0.411**	**81**	**0.034**	**15 6 15**	**5.24**	**4.21**
Right	**Limbic**	**dorsal anterior cingulate**	**area 32**	**0.717**	**0.411**	**73**	**0.043**	**14 18 27**	**4.59**	**3.83**
Right	**Limbic**	**dorsal anterior cingulate**	**area 32**					**10 16 34**	**3.91**	**3.39**
Right	Frontal	Inferior Frontal Gyrus	area 47	0.777	0.411	67	0.051	45 34 -9	4.55	3.80
Right	**Frontal**	**Inferior Frontal Gyrus**	**area 45**	**0.499**	**0.411**	**95**	**0.024**	**56 20 18**	**4.49**	**3.76**
Right	**Sub-lobar**	**Insula**		**0.757**	**0.411**	**69**	**0.048**	**42 18 0**	**4.37**	**3.69**

Table 17: Results of the analysis perceptual VS identity change. Results were significant only when contrasting Emergence 1 > Emergence 2.

4. Discussion

The present study proposed an experimental fMRI paradigm of mirror gazing that induce visual illusions ranging from changes of lights and colors to deformation of facial features and default in recognition of one's self. With a state approach we could examine brain mechanisms sustaining the emergence and ongoing activity of such illusions. The within subject design allowed us to discriminate the recruitment of brain regions underpinning the emergence of illusions, the ongoing illusions, and resting state periods without illusions. Ongoing periods were characterized by activations in occipital and frontal cortices, insula and ventral anterior cingulate gyrus, while the OFF periods seemed to recruit regions of the Default Mode Network: angular gyrus, precuneus, para-hippocampal gyrus, dorsal posterior cingulate gyrus and frontal BA10. Two other stages were of major interest; the transition between emergence and ongoing

activity of illusions, and the transition between resting state OFF periods and the emergence of illusions. The first transition seemed to be governed by activation of the dorsal posterior cingulate, while the latter involved activation of the dorsal anterior cingulate and insula. Furthermore, post-hoc preliminary analyses, showed tendentious results when comparing the emergence of perceptual changes and identity changes. It seemed that this stage was governed by regions from the salience network (anterior insula and dorsal anterior cingulate gyri).

[Brain regions sustaining the ongoing illusion period]

As mentioned above, ongoing periods of illusions are firstly sustained by activations in the occipital cortices, notably the left middle occipital gyrus (BA 18,19) and right fusiform gyrus (BA 19 and 37). It was expected that the processing of visual illusions was likely to occur in the occipital cortex, at the retinotopic level of visual representation (Hirsch et al., 1995; Weidner & Fink, 2007). However, another contribution reinforces our findings taking roots in the stream of processing of facial features. Empirical evidence suggested that the initial encoding of facial features and subsequent perceptual organization engage respectively, the occipital face area BA 18 (Pitcher et al., 2011) and the fusiform face area BA37 (Dien, 2009). Thus, activation in these regions during the illusion appear to be implicated in core steps of the facial-recognition encoding stream (Atkinson & Adolphs, 2011), not only in terms of visual recognition but also specifically in processes related to the perception of one's own face.

Imaging studies reported that the act of seeing one's own image was related to activation in the anterior insular cortex when participants viewed photos of their own faces, suggesting that activation in this region could participate in maintaining a sense of self (Devue et al., 2007). Moreover, the anterior insula has been hypothesized to be associated with emotional feelings activated by bodily changes, emphasizing the importance of internal sensations in the context of subjective experiences of emotions (Tayah et al., 2013). For instance, activation was

observed in the bilateral anterior insula during viewing of fearful faces suggesting that emotional states are integrated in the representation of the subjective feelings of the moment (Phillips, 2003). In line with previous studies, our results put into perspective that in the context of mirror gazing, activation of the insula might regulate the maintenance of the sense of self when perceiving an illusion in the specular image, while adding an emotional valence related to the subjective experience the individual is feeling while perceiving a change.

The ventral anterior cingulate (ACC) is mainly associated with emotional processing (Bush et al., 2000), notably there is consensual support for the role of ventral ACC in self-regulation or self-control including emotional but also autonomic and cognitive control (Luu, 2003; Posner et al., 2007). An interesting contribution posits a role of the ACC in the appraisal of error-detection, it is hypothesized to detect conditions under which errors are likely to occur, and helps monitoring adaptive control of behaviors (Carter, 1998; Falkenstein et al., 2000). Translated to the mirror gazing task, the ventral ACC could play a role in the detection of mismatch in the specular image triggered by the sensory deprivation effect of the set-up and participate in self-regulation of emotional experiences.

[Brain regions sustaining the resting state period without illusion]

The OFF period represents the resting state stage in which participants do not experience any illusions, it seems to involve regions of the default mode network (DMN) encompassing frontal BA10, angular gyrus, precuneus, parahippocampal gyrus and dorsal posterior cingulate (Alves et al., 2019). Corroborating our findings, the DMN showed greater activity during resting state when an individual is focused internally as oppose to the external world or attention-demanding tasks (Smallwood & Schooler, 2015). Thus, the resting state periods are characterized by a disengagement of participants from the external world when they do not experience visual illusions.

The absence of significant differences between the fading phase (a few seconds after the disappearance of the illusion) and the resting state phase, might be explained by the fact that the illusion phenomena that we measure is very brief, and behaviorally the illusion disappear as soon as participants blink their eyes. Thus, we believe there is no real fading period, that the transition between ongoing and off states might be abrupt and happens in a fraction of seconds.

[Transition between emergence and maintenance of illusions]

When contrasting the emergence and ongoing period we found an interesting result, the recruitment of the right dorsal posterior cingulate. The posterior cingulate has been associated with internally-directed cognition (Hahn et al., 2007) and is also a key node of the default mode network activated within the network during rest (Buckner et al., 2008). In the context of the transition between emergence and maintenance of illusions, we believe that the sole activation of the dorsal PCC relates more with the regulation of focus attention (Buckner et al., 2008), perhaps controlling the balance between internally and focused thoughts (Leech et al., 2011), than with the DMN-related resting state function (that requires activations of other nodes in parallel to the dPCC). Reinforcing this hypothesis, activity in the PCC was found to be modulated by arousal states and might play a role in conscious awareness (Vogt & Laureys, 2005). Thus, the transition to a maintained state of illusion might recruit processes involved in the focalization of attention towards the illusion that is perceived, and participants might become consciously aware of what they experience. Activation of the PCC could represent the starting point of the cascade of activations subsequently observed during the ongoing phase of illusions: attribution of emotional valence (insula), detection of error mismatch with anticipated face recognition (vACC and occipital) and attempt to self-regulation (vACC).

[Transition between resting state and emergence of the illusion]

The phase of transition between resting state and the emergence of illusion is of major interest, as it could give us some insight on which neural mechanisms are responsible for the trigger of illusions. We identified middle and superior frontal gyri, anterior insula and the dorsal ACC. The concomitant activation of these three regions has been associated with processes of selective attention (Weissman et al., 2006), more precisely, the anterior insula and frontal gyri would be involved in stimulus-triggered reorienting of attention, while the ACC would sustain the detection and resolution of conflicts. By detection and resolution of conflicts we mean that the dACC seems to play a specific role in detecting conflicts between simultaneously active and competing representations, and will then engage the medial prefrontal cortex to resolve such conflict (Carter & van Veen, 2007). In line with these findings, a study following brain activations in participants watching a screen on which an image was slowly revealed (Ploran et al., 2007), showed a sudden burst of activation in the anterior insula and ACC coinciding with the recognition of the percept. In terms of network modelling, it seems that the resting state is sustained by regions of the DMN, while the emergence might recruit regions of the salience network, a network responsible for the detecting and filtering of salient stimuli and for the shift between task negative and task positive networks (Uddin, 2017)

When looking at the emerging perceptual change compared to identity change, we could observe that the regions sustaining maintenance of self-recognition (perceptual change) included dorsal anterior cingulate, frontal gyri, caudate and insula. Corroborating some of our findings, Carhart-Harris and colleagues showed that the transition between normal waking consciousness and psychedelic state (as in distortions of self-consciousness) was sustained by decreased activity in anterior and posterior cingulate and medial prefrontal cortex (Carhart-Harris et al., 2012). Thus, the higher activation observed in these regions in the context of mirror-gazing, might sustain the transition between resting states and perceptual changes of the

self. Consequently, similarly to psychedelic states, a decrease activation of these regions could be hypothesized to sustain the transition between resting states and identity change. Although interesting, these results were not corrected and show a tendency, they should be confirmed with a higher sample.

Thus, we could hypothesize that the transition from resting state to emergence of illusory percept is triggered by attentional processes involving notably the reorienting of attention to the illusory input (insula/frontal). Parallel to the reorienting, the dACC activates to resolve the conflict between the resting state and this competing illusionary input (dACC), providing for recognition of the gradually revealed percept that is a change in participants' specular image. Subsequently, regions involved in the maintenance of the illusionary state will activate, followed by ongoing and processing of the vision.

[Hypothesized model of the course of visual illusions]

To sum up we propose a potential model of the neural correlates sustaining the course of visual illusions. Firstly, the transition between resting state and emergence of illusions seem to recruit the anterior insula and the dACC, responsible for the detection of conflicts between the ongoing resting state and the appearance of illusion followed or paralleled with the reorienting of attention to the stimulus that is the illusion. In addition, activations of insula and dACC seem to be responsible for the maintenance of the distinction self-other. We believe a deactivation of these regions could be responsible for the emergence of identity changes. While the illusion is emerging, activation of the dPCC plays an active role in the maintenance of the illusory phenomenon: attention is focused on the illusion that is then brought to conscious awareness. During the illusory state, occipital regions play their role in sensory visual processing, and the vACC detects the erroneous mismatch between prior knowledge anticipating self-face

recognition and the sensory deprived input. Activation of the insula might be linked to the emotional valence given to the sensory mismatch and attempt self-regulation. Finally, in the blink of an eye, regions of the task negative default mode network activate, bringing the system to resting state again.

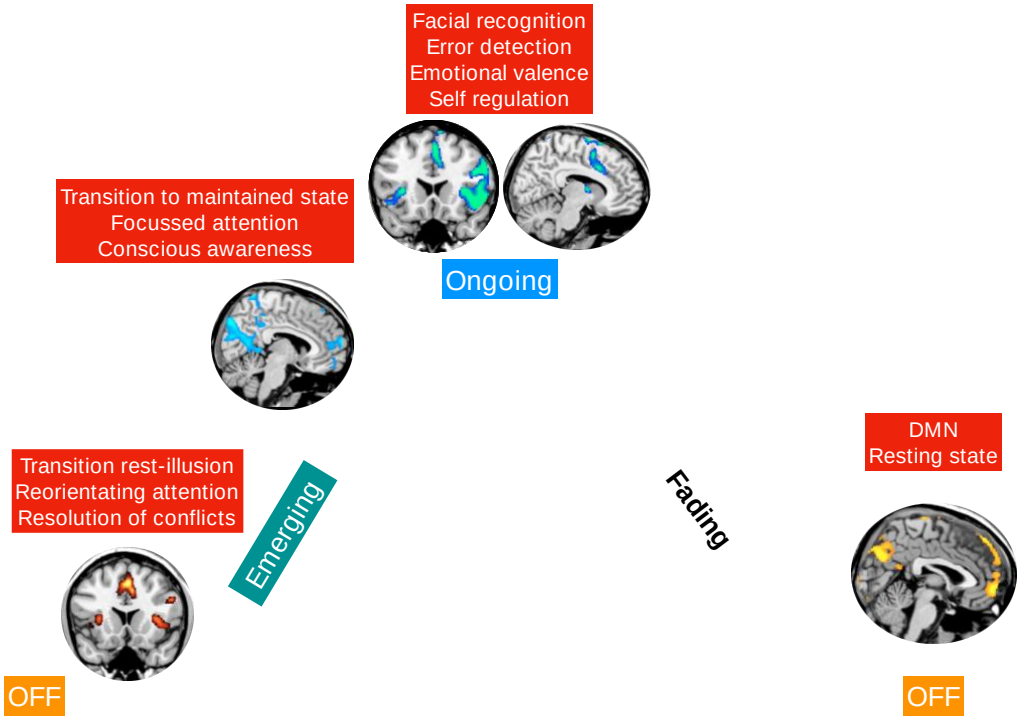


Figure 19: Hypothetical model of the course of visual illusions

5. Strength and limitations

One could think that a sample of 25 participants is a small sample to generalize neuroimaging effects, we could counter this problem with the within-subject design, actually comparing hundreds of samples per defined conditions. However, this is the first study investigating the mirror phenomena in fMRI and our results need to be replicated. Future studies should be

conducted in clinical population (such as clinical high-risk states) to confirm the link between mirror gazing task and the clinical mirror phenomena observed in psychotic symptoms.

6. Conclusion and future directions

The present study uncovers the neural underpinnings preceding and ongoing visual illusions and helps us to understand their mechanisms of appearance during the fMRI-MGT. We came up with a hypothetical model driven by our results, showing that different brain regions sustain specific stages in the course of visual illusions. Illusions can become of pathological nature (such as hallucinations) depending on whether the hallucinatory percept is either integrated in the individual's life or is considered as abnormal (Notredame et al., 2014). Thus, illusions represent an interesting tool to explore typical perception, and could provide a ground work towards the understanding of mechanisms of apparitions of pathological perceptual disturbances. Moreover, uncovering neural patterns of visual illusion provides a framework for decoding fMRI hallucination patterns, which could benefit the research on drug-resistant hallucinations and allow for innovative fMRI-based treatment, such as neurofeedback.

5. Study 5 – Resting-state networks of adolescents experiencing depersonalization-like illusions: cross-sectional and longitudinal findings[***]

Abstract

The mirror gazing task (MGT) experimentally induces illusions, ranging from simple color changes in the specular image of oneself, to depersonalization-like anomalous self-experiences (ASE) as in experiencing one's specular image as someone else. The objective was to characterize how connectivity in resting-state networks (RSNs) differed in adolescents reporting such depersonalization-like ASEs during the MGT, in a cross-sectional (Y1) and in a longitudinal manner (a year after). 75 adolescents were recruited; for the cross-sectional analysis, participants were split into 2 groups: those who reported depersonalization-like ASEs on the MGT (ASE), and those who did not (NoASE). For the longitudinal analysis, participants were split into 3 groups whether they experienced MGT depersonalization-like ASEs: only at Y1 (Remitters), both times (Persisters), or never (Controls). Participants also filled out self-reports assessing schizotypal personality (SPQ) and underwent resting-state functional MRI procedure (rs-fMRI). A group level Independent Component Analysis (ICA) was conducted and voxel-wise inter-group differences within RSNs were examined. The rs-fMRI analysis revealed lower connectivity of specific visual areas within the primary visual network (PVN), and higher connectivity of regions within the Default Mode Network (DMN) when contrasting the ASE and NoASE groups. The areas that were atypically connected within the PVN further

[***] This is a reprint of Derome, M., Fonseca-Pedrero, E., Badoud, D., Morosan, L., Van de Ville, D., Lazeyras, F., Eliez, S., Chan, R., Rudrauf, D., Schwartz, S., Debbané, M. Resting-state networks of adolescents experiencing depersonalization-like illusions: cross-sectional and longitudinal findings(2018). Manuscript published in *Schizophrenia Bulletin*. 10.1093/schbul/sby031.

presented differential pattern of connectivity in the longitudinal analysis. Atypical connectivity of visual area within the DMN at Y1 was associated with higher scores on the disorganized dimension of schizotypy at the second evaluation. The present study uncovers a subtle signature in the RSNs of non-clinical adolescents who experienced task-induced ASEs.

1. Introduction

The growing field of research focusing on early detection of psychotic disorders manifests an increasing interest toward pre-psychotic experiential anomalies that may be observable in the premorbid phases during adolescence and early adulthood. These experiential anomalies of the self have been conceptualized by some authors as anomalous self-experiences (ASE) (Sass & Parnas, 2003), which, when meeting certain frequency and intensity criteria, may also be considered as Basic Symptoms (BS) (Schultze-Lutter et al., 2012). For example, experiencing one's specular image as that of another person represents a BS measured by the Schizophrenia Proneness interview (Fux et al., 2013), and is also recognized as an ASE by the Examination of Anomalous Self- Experiences (EASE) interview (Parnas et al., 2005). Although important conceptual and methodological differences exist between the two instruments, they both converge in assessing the mirror depersonalization-like phenomena and conceive of this symptom as representing a potential risk marker for the future onset of psychosis.

Caputo and collaborators (Caputo, 2010) introduced an experimental approach to induce such mirror illusions. In Caputo's first study, 66% of 50 healthy young adults participating in the MGT reported seeing a non-human identity within the 10-minute self-face mirror-gazing task (Caputo et al., 2012). In another study, patients with schizophrenia reported more frequent and

intense strange-face apparitions during the same task. Subsequently, Fonseca-Pedrero (Fonseca-Pedrero et al., 2015) and colleagues provided a validation of the MGT in a sample of 110 community adolescents, 34.6% of which presented with clear depersonalization-like phenomena during the task. In particular, the authors found that adolescents experiencing depersonalization-like symptoms during the MGT reported higher schizotypy scores on the positive (cognitive-perceptual) and the disorganization subscales of the Schizotypal Personality Questionnaire (SPQ) (Raine, 1991). Schizotypy refers to a set of personality traits that can be measured in the general population (Ettinger et al., 2014) . Considering that the level of positive schizotypy naturally decreases during adolescence (Debbané et al., 2013) but that for youths at increased risk for psychosis, schizotypal expression remains more persistent during this period, conducting research in cohorts of typically developing adolescents may be useful to prevention studies. Indeed, such cohorts provide an opportunity to identify developmental processes implicated in vulnerability to psychosis, without the limitations of medication and other risks factors, such as comorbidities with other psychopathologies and hospitalization. Furthermore, adolescence appears to be a designated period to study the development of ASEs, as it is characterized by a profound change and consolidation of self-identity (Goth et al., 2012).

Importantly, adolescence is the theatre of crucial brain maturation. Today, little is known about the functional brain architecture of adolescents who are vulnerable to depersonalization-like phenomena. Recent neurobiological investigations have focused on examining brain changes associated with the onset of psychosis and along the psychosis spectrum (Pantelis et al., 2007). Atypical activations during self-reflective tasks appeared to be involved when participants presented high expression of positive schizotypy (Lagioia, 2010), as well as in first episode psychosis (Alonso-Solís et al., 2012) and full blown schizophrenia (Brunelin et al., 2007;

Buckner et al., 2008; Nelson et al., 2013). These atypical activations encompass areas such as medial PFC, and other midline cortical structures (anterior cingulate, superior frontal gyrus and posterior cingulate gyri) independently of the sensory modality or stimuli domain (Northoff et al., 2006). Resting state functional MRI (Rs-fMRI) studies – which evaluate functional interaction during rest – that investigate typically developing population in relation to schizotypy and distal risk for psychosis are rare. In one study, Lagioia (Lagioia, 2010), found positive correlations between visual network low frequency fluctuations and adolescents' schizotypy scores, notably with positive and disorganized dimensions. One way to start broaching the question of neural vulnerability to ASEs is to ask whether those experiencing these illusions differ in cerebral connectivity profiles, when compared to those not experiencing these illusions. To the best of our knowledge, this study is the first to examine RSNs connectivity in non-clinical adolescents experiencing task-induced ASEs. Disentangling some of the early neural mechanisms associated to depersonalization-like illusions could help uncovering the neuro-functional patterns sustaining part of the risk for psychosis. In this context, the first aim of the present study is to identify the neural signature in RSNs of adolescents experiencing task-induced ASEs. Secondly, by introducing a longitudinal dimension, we aim to investigate the link between atypical connectivity patterns and schizotypal factors after a one-year interval, and whether persisting vulnerability to experimentally-induced ASEs are linked to consistent atypical connectivity patterns.

2. Methods

2.1 Participants

The study included 75 (39 Males, 36 Female, mean age= 16.85, *SD*=2.48) native French-speaking, community adolescents and young adults with normal or corrected to normal vision. Participants were recruited by word of mouth and through advertisement at the University and schools of Geneva. Individuals were included in a longitudinal study, which comprised multiple time points. We were interested in two of these time points corresponding to the first time adolescents participated in the task (Y1), and the second time they took part in the same experiment after an interval of one year (Y2). The final rs-fMRI analysis at Y1 included the whole sample of 75 adolescents, but the longitudinal rs-fMRI analysis only comprised a subsample of them (*N*=39, 22 females and 17 males, mean age= 16.39, *SD*= 1.5) because 36 participants did not come back for Y2. Participants received a financial compensation, and written consent was obtained from participants or their parents (if they were under 18), under protocols approved by the local ethical commission (Commission Centrale d'éthique de la Recherche des Hôpitaux Universitaires de Genève). The 75 participants included in this study represent a subsample of those comprised in a previously published report (*N*=110).

2.2. Instruments: self-reported measures

At both time points, dimensions of schizotypy were measured using the Schizotypal Personality Questionnaire (SPQ, (A. Raine, 1991)). Adult Self Report (ASR) and Youth Self Report (YSR) questionnaires were also assessed to evaluate adaptive behavior in our cohort. Of interest, externalized scores on these scales reflect aggressive and rule breaking behavior, whereas internalizing behaviors include withdrawal, depression, anxiety and somatic complaints. Following Modinos and colleagues' findings (Modinos et al., 2018) - exhibiting the impact of depressive and anxiety co-morbidity on the neuroanatomy of individuals at ultra-high risk of

psychosis - scores on the two dimensions were used as covariates in each of the following statistical analysis. A summary of these measures is presented in table 19 for both the cross-sectional and the longitudinal analyses. *Questionnaires are described in the supplementary material*.

2.3. Mirror-gazing task (MGT)

Set up of the MGT

Participants faced a large mirror mounted on a tripod in a parcel of a room where the light was dimed (Figure 20). Before the beginning of the task, the experimenter gave the following instructions: "*Your task is to look at yourself in the mirror. You should keep staring into your eyes. The task will last 10 minutes". See supplementary material for more details.*

Qualitative measures

In order to characterize the nature of participants' perceptions changes, they were administered a standardized questionnaire after the mirror-gazing session ended, in which they described what they perceived in the mirror. We used these qualitative measures to identify which adolescents experienced depersonalization-like phenomenon, such as perceiving another facial identity, either human or non-human, in the mirror. The ASE and noASE groups were formed on this basis. *See supplementary material for detailed description of the methodology*.

Quantitative measures

Participants were also informed to press a button every time they experienced a variation in perception and hold it until the change disappeared, their responses were digitally recorded

through COGENT software (http://cogent.psyc.bbk.ac.uk). The event-related responses to perceptions of modifications in the specular image were recorded in terms of number and duration of abnormal perceptions (please consult the *supplementary material* for descriptions of measures).

2.4. Partition of participants in groups

Groups for the cross-sectional analysis

All 75 participants were distributed into one of two groups, on the basis of depersonalization-like phenomena they experienced, which were assessed through the questionnaire. The first group included adolescents who experienced only slight changes of color/light and/or deformation of their own faces (participants experiencing no aberrant self-experiences during the MGT = NoASE). The second group reunited participants who perceived another facial identity and/or had non-human visions (participants experiencing aberrant self-experiences during the MGT = ASE). Individuals were included into one of these groups on the basis of the most significant illusion they reported.

Groups for the longitudinal analysis

Only 39 out of the 75 participants initially included in the study came back at Y2. To explore the longitudinal trajectories of our adolescents between Y1 and Y2, we constituted three groups: The *Control group* included participants who did not report any ASE after the MGT in Y1, nor in Y2; the *Remitters* consisted in adolescents who reported ASE at Y1 MGT, but not during the follow-up visit; the *Persisters* comprised individuals reporting ASE during the MGT

task at both time points. Therefore, participants who experienced ASE at Y1 in the longitudinal analysis (Persisters + Remitters at Y1) constituted a subsample of the 30 participants reporting ASE included in the cross-sectional study. Those who were classified as Controls at Y1 in the longitudinal analysis were a subsample of the 45 who did not experience ASE in the cross-sectional analysis. A schema of the partition of participant into groups is presented in Figure 20. Only two participants did not experience ASE at Y1 but experienced ASE at Y2: they were excluded from the analyses. There was no group difference in actual time interval between Y1 and Y2 (*F=3.41, p=0.08*). Analysis of participants who did not come back at Y2 compared to those who came back displayed no significant differences (see *supplementary material).*

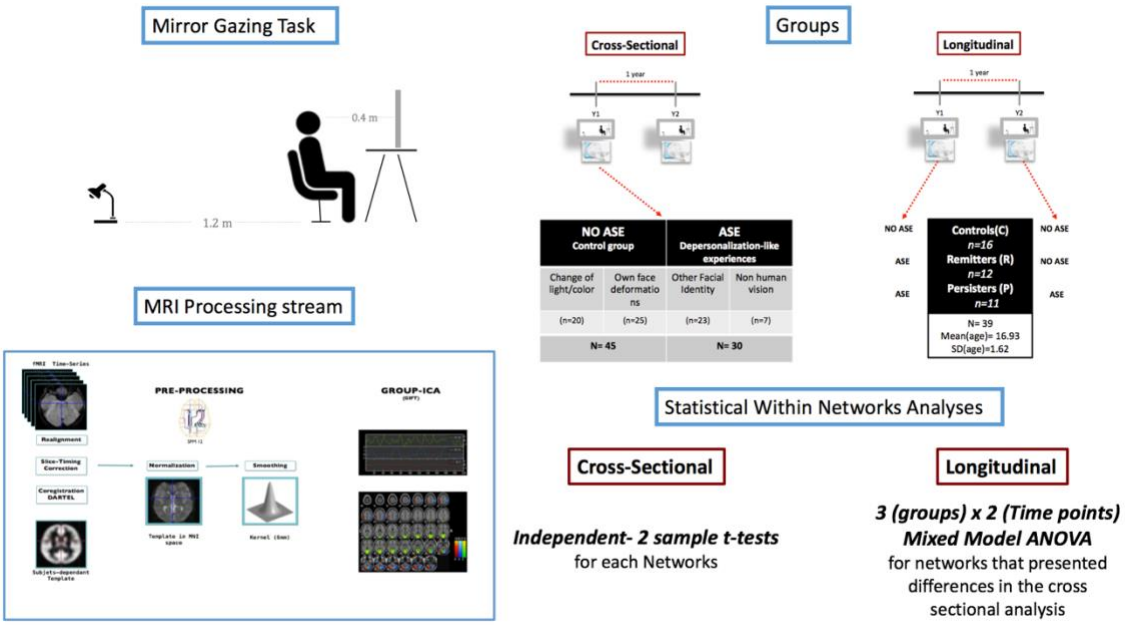


Figure 20: Methodology

The set up of the MGT is presented in the left upper corner. The partition in groups in the right corner, with their respective analyses. And the MRI processing steps are presented in the left bottom corner.

2.5. MRI Acquisition and pre-processing

Acquisition and pre-processing methods were common to both cross-sectional and longitudinal analyses.

Acquisition

Anatomical, and functional resting-state imaging data were acquired on a 3T Siemens Trio scanner. For the detailed acquisition parameters, see *supplementary material.*

fMRI Pre-processing

Functional MRI data was pre-processed using SPM12 analysis software (http://www.fil.ion.ucl.ac.uk/spm). A standard pre-processing pipeline was used, including slice timing correction, realignment, co-registration, normalization, and smoothing. None of the participants had a range of movement greater than 3 mm translation or 3 degrees of rotation, and movement parameters were regressed out at the individual level, in order to minimize biases from motion artefacts. These criteria have been widely employed in non-clinical population (Power et al., 2014; Shirer et al., 2012; Supekar et al., 2010). Furthermore, Power's Framewise Displacement (FD) was computed and mean comparison between groups (NoASE: *FD*=0.17, ASE: *FD*=0.19) did not reveal significant differences (*t(73)*=0.877*, p*=0.383). Linear detrending and bandpass filtering (0.001-0.1 Hz) were conducted using DPARSF (http://ffmri.org/DPARSF). Connectivity values were z-transformed (*see supplementary material).* For cross-sectional and longitudinal analysis, and in the correlation analysis, we co-varied for gender, demeaned age (mean centering), and standardized externalized and internalized scores.

2.6. Cross-sectional statistical analysis of rs-fMRI data

rs-fMRI analysis

Group-level spatial ICA was conducted on the entire sample of participant (*N*=75) using GIFT toolbox implemented in Matlab (http://mialab.mrn.org/software/gift). ICA technique allows the separation of spatio-temporal BOLD signal into spatially statistically independent components (ICs) (Beckmann & Smith, 2004). The Infomax ICA (Bell & Sejnowski, 1995) algorithm was run 50 times in ICASSO and resulting components were clustered to estimate the reliability of the decomposition – the index I_q, ranging from 0 to 1 (Himberg et al., 2004), was greater than 0.9 for each component. Ten components were visually identified as RSNs (*supplementary Appendix 6 figure 1*) and confirmed using correlations computed between the components and resting-state network templates (http://findlab.stanford.edu/functional_ROIs.htlm, *see Appendix 6).*

Group differences within networks

To test for differences among groups within each network, we fed the spatial maps of the independent components from participants into 2 independent samples *t* test. A full factorial analysis was completed in SPM12 for each component. We generated contrasts between ASE and noASE, from which we extracted significant clusters exhibiting peak activity (*t*-values) passing FWE-correction (Nichols & Hayasaka, 2003) (family wise error) $p<0.05$.

Group differences between networks

To investigate variations of inter-network connectivity, we constructed a connectivity matrix per group (Nparticipants x NICA x NICA). Functional connectivity between pairs of ICs was assessed using partial correlations, resulting in a 10 x 10 matrix in which each element represented the connectivity strength between two ICs. Statistical analysis was conducted using 2-sample t-test for each connection. Acceptance criteria of the results included a threshold of $p<0.05$, FWE-corrected for multiple comparisons.

2.7. Longitudinal statistical analysis of rs-fMRI data

rs-fMRI analysis

The rs-fMRI longitudinal analysis was conducted using the same method and parameters we employed for cross-sectional analysis. Group ICA was conducted on 78 sessions because each participant (N=39) had two time points and each time point was considered as a single session. This method - reducing the risk of missing components that are only present at Y2 and decreasing ICA algorithmic variability - was employed in previously published longitudinal study (Damaraju et al., 2014).

Analysis of the interaction groups x time points within networks

The longitudinal analysis focused on networks that presented differences in the cross-sectional analysis. We tested for within-network connectivity differences in regions within the primary visual network (PVN) and default mode network (DMN) among groups, time points as well as the effect of their interaction. To do so we fed, on one hand, the spatial maps of the dDMN and on the other hand of the PVN from all participants into two separate mixed model ANOVAS

(Beckman et al., 1987). The statistical analysis was implemented in SPM12 for each component and consisted in a 3 (groups) x 2 (time points) design. We generated *F*-contrasts to assess main effects and interactions and post hoc *t*-contrasts to identify the direction of those effects. We retained significant clusters exhibiting peak activity (*t*-values) passing FWE-correction for multiple comparisons at the voxel level, $p<0.05$. Moreover, a Bonferroni correction for multiple analyses was computed with a criterion of $p<0.025$.

2.8. Correlation with clinical data

In order to investigate the relationship between within network connectivity differences at Y1 and the evolution of SPQ dimensions on the one-year interval, mean voxel values were extracted using Marsbar toolbox from each participant. We extracted these values within ROIs at MNI coordinates corresponding to peak *t* values from clusters that had passed the FWE correction of $p<0.05$ in the cross-sectional analysis. The mean voxel values thus represented the strength of the cluster expressed at a spatial location within the network. We then computed the difference of scores between Y1 and Y2 for each of the dimensions of the SPQ, which we correlated to the strength values. Spearman partial correlation for non-parametric analysis was used. Results were retained at a threshold of $p<0.05$ and Bonferroni correction for multiple comparisons was applied.

3. Results

3.1. Descriptive measures

Variables	Whole sample	No ASE	ASE	Statistics ASE vs NoASE	Effect size (d)
N	75	45	30		
Age	16.85 +/- 2.48 (12-24)	17.1 +/- 2.91 (12.15-24.86)	16.47 +/- 1.61 (12.32-19.47)	t=1.21, p=0.231	(0.2)
Gender	36 Females 39 Males	22 Females 23 Males	14 Females 16 Males	Chi-square=.120, p=0.729	
Externalizing scores	54.91 +/- 10 (30-76)	52.67 +/- 10.1 (30-73)	58.46 +/- 9.2 (40-76)	t=-2.447, p=0.017*	(-0.6)
Internalizing scores	52.21 +/- 10.6 (32-82)	51.31 +/- 9.98 (32-68)	53.79 +/- 11.54 (32-82)	t=-0.911, p=0.365	(-0.2)
SPQ-Positive	7.05 +/- 6.16 (0-27)	5.44 +/- 4.49 (0-18)	9.46 +/- 7.51 (0-27)	U=420, p=0.006**	(-0.6)
SPQ-Disorganized	5.0 +/- 3.70 (0-16)	4.39 +/- 3.45 (0-13)	6.09 +/- 3.92 (0-16)	U=444, p=0.012*	(-0.5)
SPQ-Negative	5.66 +/- 4.24 (0-18)	5.2 +/- 4.0 (0-14)	6.36 +/- 4.56 (0-18)	U=553, p=0.186	(-0.3)
Mean Duration	6.01 +/- 15.68 (0-135.98)	4.63 +/- 8.6 (0-40.7)	8.65 +/- 22.84 (0-135)	U=661, p=0.038*	(-0.2)
Cumulative Duration	86.7 +/- 126.5 (0-815)	0.13 +/- 0.18 (0-1.04)	0.18 +/- 0.25 (0-1.36)	U=534, p=0.188	(-0.2)
First Onset	53.7 +/- 82.6 (0-480)	43.05 +/- 62.66 (0-276)	71.82 +/- 107.4 (0-480)	U=527, p=0.163	(-0.3)
Frequency	16.7 +/- 15.6 (0-59)	0.025 +/- 0.028 (0-0.98)	0.03 +/- 0.023 (0-0.08)	U=515, p=0.190	(-0.2)

Variables	Whole sample (N=39)	Controls (N=32)				Persisters (N=22)				Remitters (N=24)				Chi-square Test
		Y1	Y2	Stats	d	Y1	Y2	Stats	d	Y1	Y2	Stats	d	
N	78	16	16			11	11			12	12			
Age	16.92 +/- 1.65 (12.33-20.31)	16.25 +/- 1.4 (12.7-18-8)	17.78 +/-1.57 (14.2-20.3)	t=-12.76, p=0.00**	(-1)	16.3 +/- 1.28 (13.5-17.9)	17.65 +/- 1.36 (14.36-19.12)	t=-12.32, p=0.00**	(-1)	16.35 +/- 1.8 (12.33-19.04)	17.41 +/- 1.82 (13.48-20.07)	t=-27.53, p=0.00**	(0.6)	
Gender		9 Females 7 Males				7 Females 4 Males				6 Females 6 Males				Chi-square= 0.434, p=0.805
Externalizing scores	57.58 +/- 9.1 (34-77)	56.25 +/- 8.3 (42-73)	52.9 +/- 8 (34-63)	t=1.07, p=0.30	(0.4)	56.45 +/- 8.74 (40-70)	58.09 +/- 8.64 (45-71)	t=-0.87, p=0.4	(-0.1)	61.92 +/- 10.6 (38-76)	60.25 +/- 9.3 (48-77)	t=0.717, p=0.48	(0.2)	
Internalizing scores	53.78 +/- 9.42 (32-82)	54.19 +/- 8.49 (40-68)	50.42 +/- 10 (36-69)	t=0.43, p=0.67	(0.4)	53.91 +/- 14.2 (35-82)	57.55 +/- 6.2 (45-65)	t=-1.15, p=0.27	(-0.3)	54.58 +/- 9.34 (32-66)	52.25 +/- 5.9 (44-67)	t=0.706, p=0.49	(0.3)	
SPQ-Positive	7.65 +/- 5.6 (1-27)	5.75 +/- 3.1 (2-12)	4 +/- 2.9 (1-10)	t=1.57, p=0.14	(0.6)	12.64 +/- 9.3 (1-27))	7.55 +/- 5.13 (2-19)	t=2.72, p=0.02*	(0.7)	9.5 +/- 5.4 (2-21)	7.5 +/- 2.9 (3-12)	t=1.2, p=0.24	(0.5)	
SPQ-Disorganized	5.41 +/- 3.46 (0-16)	4.5 +/- 2.7 (0-9)	2.08 +/- 2.15 (0-6)	t=3.74, p=0.003**	(1)	7.82 +/- 4 (2-16)	6.09 +/- 3.3 (2-12)	t=1.8, p=0.1	(0.5)	5.67 +/- 3.34 (0-13)	6.83 +/- 2.55 (2-11)	t=-1.48, p=0.17	(-0.4)	
SPQ-Negative	6.22 +/- 4.2 (0-18)	5.31 +/- 3 (0-10)	5.08 +/-4 (0-15)	t=0.0, p=1	(0.06)	8.09 +/- 5.8 (0-18)	7 +/- 5.4 (0-14)	t=1.3, p=0.22	(0.2)	6.08 +/- 3.42 (2-11)	6.25 +/- 3.46 (1-13)	t=-0.29, p=0.77	(-0.05)	
Mean Duration	4.67 +/- 6.44 (0-40.7)	5.28 +/- 9.8 (0-40.7)	3.54 +/- 4.4 (0-12.6)	Z=-0.72, p=0.47	(0.2)	6.16 +/- 8.2 (0-2821)	3.72 +/- 5.6 (0-20.13)	Z=-1.96, p=0.05	(0.3)	5.06 +/- 3.46 (0.48-11.61)	4.11 +/- 3.9 (0-15.05)	Z=-1.02, p=0.31	(0.2)	
Cumulative Duration	0.15 +/- 0.16 (0-0.7)	0.15 +/- 0.17 (0-0.5)	0.13 +/- 0.15 (0-0.5)	Z=-0.28, p=0.78	(0.12)	0.19 +/- 0.19 (0-0.7)	0.12 +/- 0.16 (0-0.57)	Z=-1.87, p=0.06	(0.4)	0.17 +/- 0.11 (0-0.3)	0.15 +/- 0.18 (0-0.65)	Z=-0.86, p=0.38	(0.1)	
First Onset	53 +/- 98 (0-480.9)	39.9 +/- 56 (0-229)	91.8 +/- 167 (0-473)	t=-0.16, p=0.87	(-0.4)	40.74 +/- 51.97 (0-180)	18.13 +/- 13.32 (0-38.71)	Z=-0.98, p=0.33	(0.6)	70.17 +/- 131 (6.86-480.9)	58.07 +/- 87.9 (0-309.9)	Z=-0.31, 0p=0.75	(0.1)	
Frequency	0.03 +/- 0.02 (0-0.11)	0.03 +/- 0.03 (0-0.9)	0.03 +/- 0.03 (0-0.11)	Z=-1.0, p=0.31	(0)	0.03 +/- 0.02 (0-0.06)	0.03 +/- 0.02 (0-0.06)	Z=-0.25, p=0.8	(0)	0.03 +/- 0.02 (0-0.08)	0.03 +/- 0.02 (0-0.06)	Z=-0.16, p=0.87	(0)	

Table18: Descriptive measures for participants of the cross-sectional analysis on the top, and the longitudinal analysis on the bottom

Descriptive measures are presented in table 19 for participants of both the cross-sectional and longitudinal analysis (see *supplementary material for more details)*.

3.2. Identification of functionally connected neural networks

After running ICA, we retained 10 networks; their spatial maps are shown in Appendix 6 *Supplementary figure 1* and coordinates of their peak activations are presented in supplementary-table1.

3.3. Cross-sectional results: Group differences within and between networks

Group contrasts revealed significant differences in functional connectivity between noASE and ASE groups (Figure 21). Lower within-network connectivity in the ASE group relative to NoASE (NoASE > ASE) was observed in sub clusters of the primary visual network (PVN), more precisely in the right fusiform gyrus (BA 37, t=5.33, p=0.038) and the right superior parietal lobule (BA7, t=5.51, p=0.016). In contrast, individuals who experienced depersonalization exhibited greater within network connectivity (ASE > noASE) in sub clusters of the ICA component associated with the dorsal default mode network (dDMN), in non-typical regions of the network, the left middle occipital gyrus (BA 18, t=5.90, p=0.003). Between networks analysis did not yield any statistically significant results.

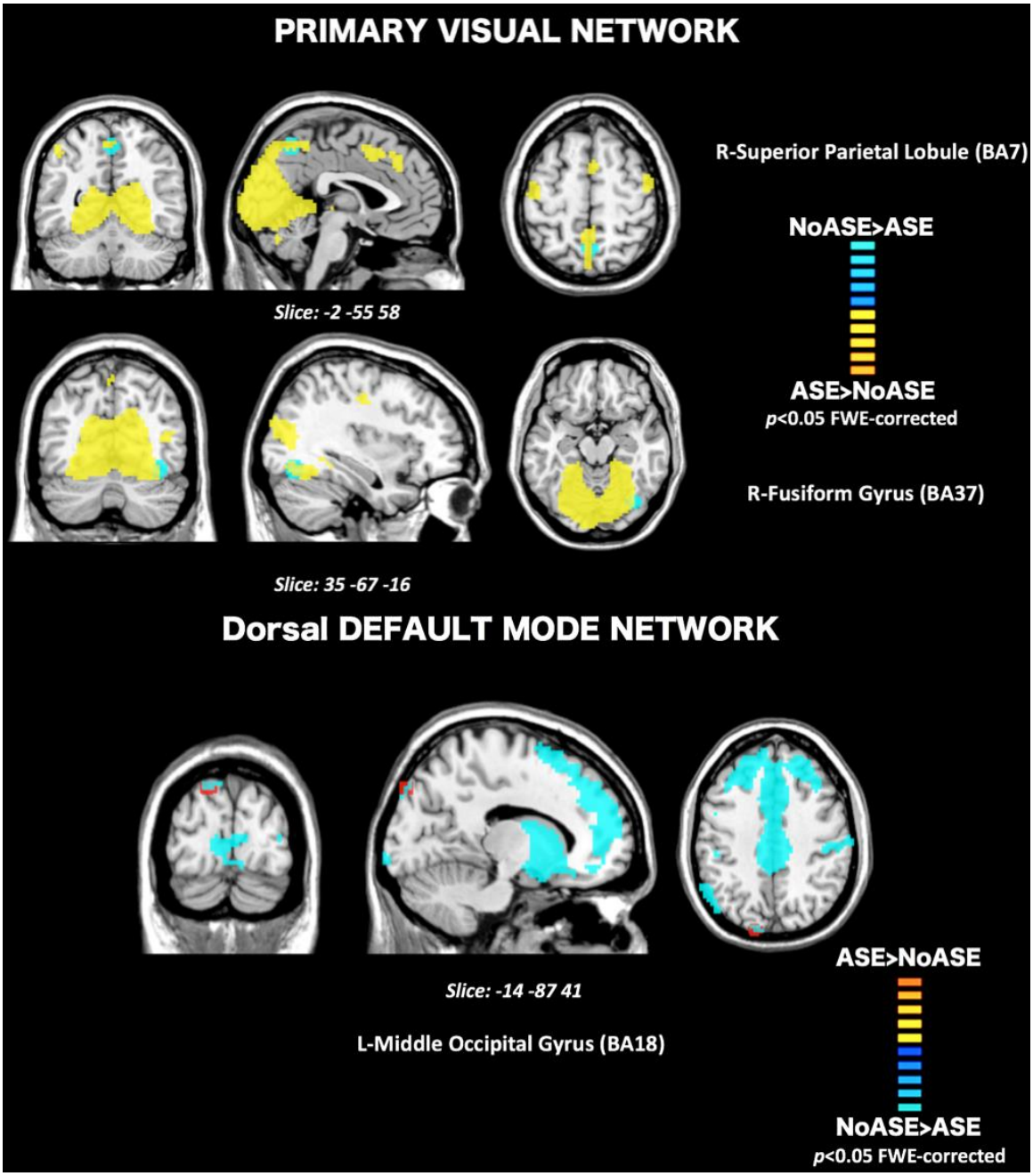


Figure 21: Cross sectional results

3.4. Longitudinal results: Group x Time point differences within networks

Group contrasts from the mixed model ANOVA revealed a significant effect of group x time points interaction on the connectivity of regions corresponding to two Brodmann areas within the PVN. From Y1 to Y2, connectivity of the right lateral occipital gyrus (BA19) was decreased in the Persisters's group, whereas it was increased in the Remitters' group (t=5.67, p=0.015 *FWE-corrected*). Furthermore, connectivity of the left posterior inferior temporal gyrus (BA20) within the PVN was increased from Y1 to Y2 in the Persisters and decreased in the Remitters (t=5.34, p=0.015 *FWE-corrected*, Figure 22). These results remained significant when applying Bonferroni correction. No significant differences were found when investigating the dDMN.

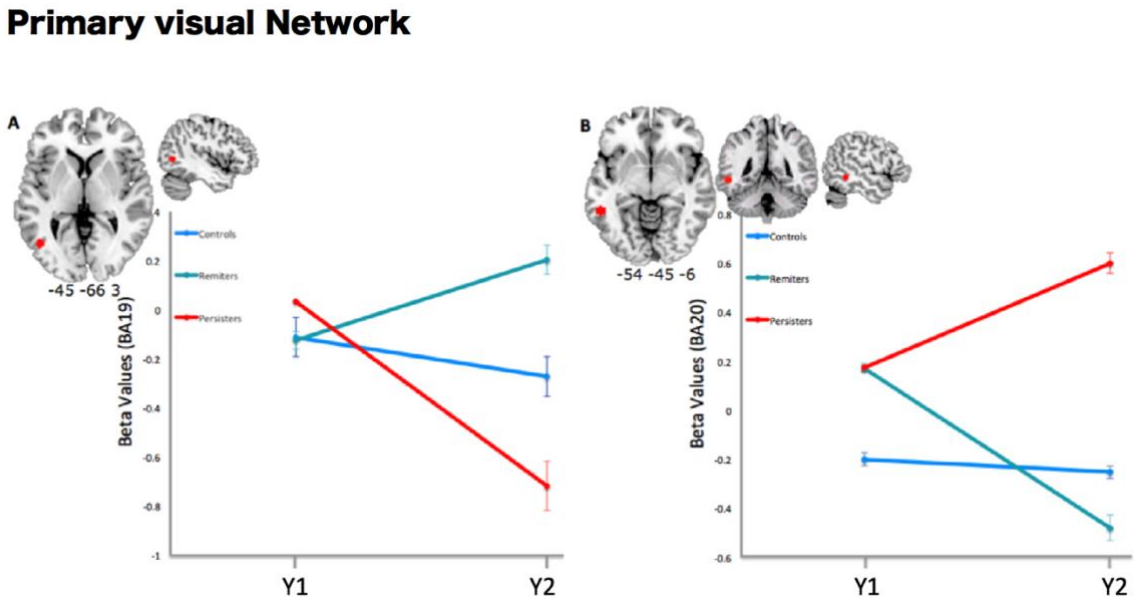


Figure 22: Longitudinal results

3.5 Correlation with clinical data

Correlations between mean voxel values extracted from ROIs at Y1 (BA 18, BA 7 and BA 37), and, the evolution of SPQ dimensions during the one-year interval (Y2-Y1) did not reveal significant association when analyzing the whole sample, or when analyzing only the control group. However, in the ASE group, mean connectivity of area 18 was positively correlated with the SPQ disorganized dimension (*Rho*=0.546, *p*=0.006). This result survived the Bonferroni correction for multiple comparisons. Therefore, the atypical connectivity of the middle occipital gyrus related to the ICA component associated with the dorsal DMN of the ASE group observed at Y1 appears to be associated with increasing scores on the disorganized dimension of schizotypy when considering an interval of one year (Figure 23). No association was found between ROIs resulting from the interaction groups x time points and SPQ dimensions.

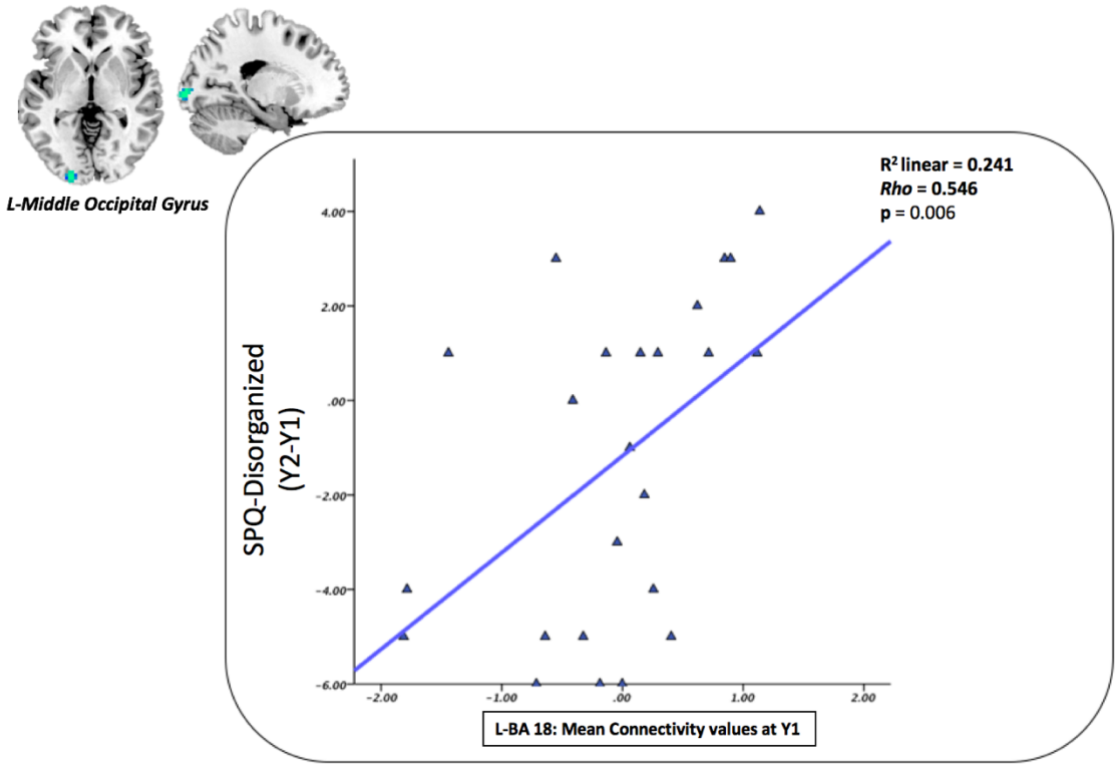


Figure 23: Correlation with clinical data

4. Discussion

We employed the Mirror Gazing Task (MGT) to characterize proneness to depersonalization-like anomalous self-experience (ASE), in a cohort of typically developing adolescents. Based on their reports of ASEs during the MGT, adolescents were split into two distinct groups for the cross-sectional analyses, and into three for the longitudinal analyses. Each participant also underwent a Resting State Functional MRI scan (rs-fMRI). Using ICA, we identified three areas presenting differences between the two groups (ASE and noASE): the right fusiform gyrus (FG, BA37) and superior parietal lobule (SPL, BA7) related to the Primary Visual Network ICA component, and the left middle occipital gyrus (m-OG, BA18) related to the dorsal Default Mode Network (DMN) ICA component. The longitudinal analysis yielded differences between ASEs Persisters and Remitters in the left inferior posterior temporal gyrus (ip-TG, BA20) and the left lateral OG (l-OG, BA19) as related to the PVN component. The following discussion will firstly address the results of the cross-sectional, and secondly those of the longitudinal rs-fMRI analyses, in line with existing literature on rs-networks and self-referential processing in psychosis-prone and patients with psychosis.

Concerning the cross-sectional results, at the network level, we observed a lower connectivity within the PVN-related ICA component involving the right FG and the right SPL. Furthermore, we found a greater connectivity of the m-OG with the DMN-related ICA component of adolescents experiencing ASEs. Empirical evidence suggests that the initial encoding of facial features and subsequent perceptual organization primarily engage the occipital face area

(BA18, (Pitcher et al., 2011)) and fusiform face area (BA37, (Dien, 2009)). Therefore, areas presenting subtle connectivity alterations appear to be implicated in core steps of the face-recognition processing stream (Atkinson & Adolphs, 2011). This could partly explain why adolescents expressing these subtle alterations would be more prone to experience depersonalization phenomena induced by the MGT. Early perceptual organization (Uhlhaas & Silverstein, 2005) impairments may disorganize the articulation of sensory information into coherent representations, and constitute an initial step to self-experienced perceptual deficits described by patients with schizophrenia (Albers et al., 1998).

These findings may also be discussed at a conceptual level. From the standpoint of Northoff's model of self, three different layers of processing may be distinguished on the basis of results from meta-analyses (Northoff et al., 2006): sensory processing related to the "bodily self" sustained by the sensory cortex; pre-reflective self-referential processing is referred to as the "minimal self" and is associated with medial cortical connectivity; and higher order processing linked to the cognitive aspects of self-processing, such as autobiographical and emotional aspects of self which are related to the lateral cortex. Our results seem to corroborate a connection between self-referential processing and sensory (visual) processing in the experienced modification of one's own face. We speculate that the MGT could induce a conflict between sensory and self-referential processing, underpinned by the subtle alteration of functional connectivity involving components associated with the PVN and DMN. Alternatively, the atypical connectivity patterns might lead to a disconnection between the two aspects of the self in the model, i.e. bodily and pre-reflective selves. A recent study showed that gazing at one's self in the mirror increases the consciousness about bodily self. However, in a context of sensory deprivation, in participants experiencing ASE, bottom-up regulation (e.g. from bodily to reflective self) could be disconnected, inducing interruption of self-face

recognition, while overweighting top-down modulation (reflective to bodily self), in a manner that could generate the illusion.

The longitudinal analysis did not yield a strict anatomical correspondence with respect to the cross-sectional analysis, as differences between groups were found in the left ip-TG (BA20) and the left l-OG (BA19) in relation to the PVN component. However, the corresponding Brodmann areas are functionally consistent with those highlighted in the cross-sectional analysis. Both sets of areas may have complementary though slightly different functions: for instance, the left BA20 has been implicated in visual fixation (Richter et al., 2004), whereas the right FG determines whether recognized "face-like" features belong to an actual face. Area 18 is implicated in the detection of light (Mentis et al., 1997) and pattern, while area 19 play a role in human object recognition (Grill-Spector et al., 2001). Importantly, the longitudinal results showed differential patterns of connectivity between the Persisters and the Remitters, meaning that atypical connectivity of these areas implicated in visual processing streams, either persist or remits at the one-year follow-up.

The link between schizotypy and RSNs was supported by a positive correlation between the connectivity of the R-mOG in relation to the DMN at Y1 and the evolution of scores on the disorganized dimension of schizotypy. These results are consistent with those reported by Lagioia and colleagues on an independent sample, finding positive correlations between VN low frequency resting-state fluctuations and adolescents' schizotypy scores, notably pertaining to positive and disorganized dimensions (Lagioia, 2010).

From a theoretical standpoint, it is relevant to invoke and build upon recent Bayesian models of schizophrenia's positive symptoms in order to interpret our results. In this model, positive

symptoms are conceived as reflecting poor precision in prior beliefs about the causes of sensory inputs (Adams et al., 2013). Trait abnormalities would result from an inadequate relative precision of prior beliefs and sensory evidence (Corlett et al., 2011). We could hypothesize in our context, that cognitive priors about our own face direct attention towards sensory features based on top-down modulation of sensory precision. Considering the MGT as inducing a situation of under-stimulation analogous to sensory deprivation, sensory evidence cannot contribute to posterior information, which implies that perceptual inference is mostly based on priors. The precision of cognitive priors is updated to compensate for the decrease of sensory precision and could be leading to perceptual illusions. Assuming adolescents experiencing ASEs present atypical priors, differences in the degree of failure to attenuate the weight of their own faces' priors – meaning to attenuate the corollary discharge of self-made face-priors – might explain the varying degrees of depersonalization.

We may notice some of the rs-fMRI results discussed above appear outside of the anatomical regions typically associated with such rs-network ICA components. Inter-group differences were revealed in the m-OG and the SPL, which are not originally included in the traditional definition of respectively, the DMN and the PVN. However, the results appear robust: group-ICA performed on the whole sample of our adolescents ascertained the presence of differences in the signals from the components associated with these networks with peak values surviving a stringent statistical threshold (p<0.0001 *FWE-corrected, see supplementary-table1*). Analyses were performed per ICA component, and the strength of the resulting contrasts supports the hypothesis that they represented an actual effect rather than noise. The results thus highlight regions that may have a significant functional role in connection to components and networks featuring a core anatomy that does not typically engage them (Philippi et al., 2015; Soto et al., 2018).

These results must be interpreted in light of the following limitations. Firstly, as the task was performed outside the scanner, rs-fMRI represents an indirect measure. Future studies should provide a direct measure of the emergence of ASEs, at the exact moment at which they appear, using an fMRI task. Secondly, our cohort is constituted of typical adolescents, thus, further inquiry is necessary on other risk cohorts, such as individuals experiencing BSs and/or at ultra-high-risk states.

Findings of the present study suggest that subtle atypical within-network connectivity, involving sensory and self-referential networks, is linked to susceptibility to experience induced ASEs. Further research concerning the mechanisms at stake in the emergence of ASEs could potentially reveal phenomenological and biological markers for vulnerability to psychosis.

Chapter IV

Discussion

This final chapter summarizes and draws the findings together. This chapter also includes discussions on the implications of the research in terms of existing literature and clinical relevance, the limitations of the studies and suggests future directions for research.

1. Summary of the conducted studies

The main hypothesis for studies 1 and 2 is that since schizotypy can be considered a part of the extend phenotype of broadly defined schizophrenia, it should share similar characteristics, notably brain structural changes. The second half of the thesis, with studies 3, 4 and 5, investigated anomalous self-experiences as a non-clinical state that could inform the development and mechanisms of apparitions of visual hallucinations observed in the schizophrenia spectrum.

1.1.1 Conclusion Study 1

To date, there are only a few studies investigating the brain correlates of schizotypy in the general population, yielding disparate results. Adults' population studies have shown grey matter volume decreases in frontal, temporal and cingulum cortices (DeRosse et al., 2015; Wiebels et al., 2016). Whereas studies on adolescent populations are rare, and to the best of our knowledge, mostly cross-sectional. The prospective study we conducted examined developmental trajectories of cerebral endophenotypes of cortical thickness during adolescence. This study disentangled the extent to which structural brain differences conveyed

part of the vulnerability to schizophrenia spectrum disorders, or whether they were linked to interindividual variability on the schizotypy trait. Using Mixed regression models approach and including data from 109 adolescents with 1 to 5 time points of visits, our sample culminated to 271 scans. Major findings showed an association between positive schizotypy and accelerated thinning in the posterior cingulate cortex, while disorganized features were linked to atypical trajectories within the anterior cingulate region. Finally, atypical developmental trajectory of cortical thickness was found in prefrontal, occipital and cingulate cortices in adolescents expressing higher level of negative features. Identifying the similarities with clinical-high risk patients who transitioned to psychosis, and in conjunction with clinical evidence (Flückiger et al., 2016), we hypothesized that the negative dimension of schizotypy conveyed a potential risk-predictive value compared to the other dimensions. Notably prefrontal alterations associated to the negative dimension were considered to speak directly to emerging risk states and conversion to psychosis.

1.1.2 Conclusion Study 2

Study 2 is similar to study 1 in terms of analysis but in this study, we investigated developmental trajectories of subcortical structures volumes in relation to schizotypy. Existing literature investigating adolescents from the general population expressing high schizotypal features found relative consensus on volumetric enlargement in the lateral ventricle, hippocampus and caudate (Kühn et al., 2012; Okada et al., 2018), although there is a lack of longitudinal studies in this field. In this context the second study investigated dynamic changes in subcortical structures development in relation to the three dimensions of schizotypy of 110 adolescents (272 scans) who were included in study 1 as well. Expression of higher level of disorganized schizotypal features was associated with reduced volume of hippocampus and pallidum, and enlargement of lateral ventricle. Negative schizotypy was associated with

increased thalamic volumes and reduced volume of the pallidum. We hypothesized that higher levels of negative and disorganized schizotypy during adolescence could be linked to subtle developmental changes reflecting a neural signature at the non-clinical level, notably the hippocampus.

1.1.3 Conclusion Study 3

In the line of research focusing on early detection, an increasing interest has grown towards pre-psychotic anomalies that may be observable before the premorbid phases during adolescence. ASEs have been linked to the risk of developing schizophrenia (Koren et al., 2013; Nelson et al., 2012), while offering a different point of view from schizotypy. We could study this risk through the lens of the state, or phenomenon as related to symptoms of self-disturbances. Moreover, we proposed a developmental study included 216 children, adolescents and adults from the community (7 to 28 years old). Reviewing the handful of studies using the mirror gazing task to induce states of ASEs, we observed that the propension to experience such perceptual illusions was potentialized by positive and disorganized schizotypy, but this hypothesis needed further confirmation. Furthermore, there was a lack of information on how the propensity to experience ASEs was developing between childhood and adulthood. We aimed at establishing the developmental trajectory of proneness to ASEs and investigate the dynamic relationship with schizotypal features. To our knowledge, this would be the first study to examine non-clinical ASE-like states in children. Firstly, the present study confirmed the developmental trajectory of SPQ dimensions, showing a peak during adolescence. Secondly, it provided support that proneness to ASEs-like self-disturbances seemingly follow the trajectory of schizotypy dimensions, increasing in the adolescent population although already observable in childhood. Thirdly, we argued that positive and disorganized self-reported schizotypy seem to potentialize the proneness to induced-ASEs.

Lastly, we built an integrative model, showing significant differences in positive schizotypy between children and adolescents experiencing ASEs, while disorganized features did not play a role in this ASE-group. This result seemed to confirm the importance of positive schizotypy for the development of the risk to develop self-disturbances, in particular during the transition from childhood to adulthood.

1.1.4 Conclusion Study 4

The neuropathological mechanism of hallucinations remains unclear, as a result of the complexity of scanning cerebral activation during hallucinations. Thus, we came up with the fourth study that measured brain activations during illusions triggered by the 10 minutes MGT. The MGT was adapted to a functional MRI task, and using the response button, we could record exactly when participants would experience an illusion, and we defined emergence, ongoing and off periods of the course of illusions. The aim of this study was to uncover the neural underpinnings preceding and ongoing visual illusions in order to understand their mechanisms of appearance. We identified activations of occipital and frontal regions and most importantly of the insula while the illusion was ongoing. Mostly regions of the default mode network (DMN) during rest/off periods. The transition between resting state OFF periods and emergence of illusions was characterized by activation of the dorsal anterior cingulate cortex and insula. While the transition between emergence and ongoing activity of illusions was governed by activations in the dorsal posterior cingulate. Therefore, it seems that the course of induced ASEs is characterized by different periods associated with specific activations for each period. Furthermore, post-hoc analyses showed tendentious results when comparing the emergence of a perceptual change (deformation of one's own face) and identity changes (vision of another identity). It seemed that this transition was governed by regions from the salience network (anterior insula and dorsal anterior cingulate). We proposed a hypothetical model of

the course of illusions, with the transition rest-illusion involving reorienting of attention, the transition to maintained state recruiting regions involved in conscious awareness, ongoing periods involving error detection and self-regulation, and OFF periods recruiting regions from the task-negative network. We concluded in terms of predictive coding, suggesting that dACC would update predictions following the error signal (sent to attest for under-stimulation of the sensory input), and would allow for self-recognition (perceptual changes). Whereas absence of activation of the dACC (or deactivation), potentially lead to the experience of identity changes.

1.1.5 Conclusion Study 5

This last study completes the two preceding, by providing additional information about the functional brain architecture of adolescents who are vulnerable to depersonalization-like phenomena. Atypical activations of self-reflective tasks have been shown in patients with FEP or full blown schizophrenia (Alonso-Solís et al., 2012; Nelson et al., 2013), as well as in individuals with higher expression of schizotypy (Lagioia, 2010). The aim of this study was to identify the neural signature in resting-state networks of adolescents expressing anomalous self-experiences (depersonalization-like) illusions. We believe disentangling some of the early neural-mechanisms associated to task-induced ASEs could uncover the neuro-functional patterns sustaining parts of the risk for psychosis. Moreover, we introduced a longitudinal dimension to investigate the link between atypical connectivity patterns and schizotypal factors, to see whether persisting vulnerability to ASEs could be linked to consistent atypical network connectivity patterns. This study included 75 participants who were first grouped in ASE or no ASE at baseline. And secondly for the longitudinal analyses, we compared controls, remitters and persisters after a one-year interval. We observed decreased connectivity within the primary visual network, and increased connectivity within the default mode network for adolescents experiencing ASEs at baseline. Finally, the link between schizotypy and ASEs was

supported by a positive correlation between the longitudinal evolution of disorganized schizotypal features and regions of the DMN at baseline. Findings suggested subtle atypical within-network connectivity, involving sensory and self-referential networks was potentially linked to proneness to experience ASEs.

1.1.6 Summarizing the findings

In summary, the hypothesis that schizotypy is part of the continuum of schizophrenia and would have similar profile in term of biological correlates is supported. Increased schizotypal levels are associated with changes in brain structure similar to clinical groups, although attenuated. However, in studies 1 and 2 we could differentiate alterations in regions that were common to the spectrum and those that conveyed predictive power for the risk to develop schizophrenia. As seen in the literature and confirmed in study 3, schizotypal features seem to naturally fade away after adolescence, suggesting that there could be two forms of schizotypy: a form where features are on a continuum with mental illness and a form representing the expression of inter-individual differences in terms of personality. Targeting negative features may therefore identify younger participants more closely linked with risk for transition. In addition, prefrontal regions seem to represent a candidate for development of the risk of transition to psychosis, as well as the hippocampus when associated with disorganized schizotypy.

Studies 3 to 5 examined the link between proneness to experience ASEs and schizotypy, through developmental and neuroimaging investigations. We could observe that proneness to experience ASEs was increased during adolescence, similarly to the developmental trajectory of self-reported schizotypy. And that the positive dimension represents a potential candidate for the development of the risk to develop self-disturbances, particularly along the transition from childhood to adulthood. Additionally, modelling the course of induced-ASEs, we

identified activation patterns in different regions that are commonly altered along the spectrum of schizophrenia. The emergence of ASE showed activation in regions involved in novelty, followed by self-consciousness/referencing related regions during the illusion, and the Off period was characterized by DMN involvement, suggesting that any alterations of the regions implicated could lead to the development of self-disturbances. More importantly, tendentious results provided insight in the transition toward a perceptual or an identity change, seemingly sustained by activations of regions implicated in resolution of conflict between the sensory-deprived percept and the error signal sent by the mismatch with endogenous priors. Lastly, we could identify a subtle neural signature of induced-ASEs; atypical network of interconnected regions at rest involved the DMN, and disorganized schizotypy seemed to be linked to the persistence of ASEs after one-year.

2. General discussion

This thesis investigates the evolution of the risk to develop psychotic disorders during non-clinical phases. With the use of a trait-state approach looking at the relationship between two features that can relate to psychotic disorders (schizotypy and anomalous perception of the self) we could provide further insights for the field of early detection. The overarching goal was to take one symptom observable in high-risk states, and to understand how personality could provide a fertile ground for the expression of such phenomena. Two aspects of these features were reviewed in the existing literature and assessed in the different studies; the first one was related to schizotypy and its role in conferring a risk to develop high-risk states, the second one took roots in the continuum from illusions to hallucinations. The two fist studies broaden the knowledge on cerebral morphology correlates of schizotypal traits and allow us to differentiate the individual role of each dimensions. The third study bridges the gap between schizotypal personality traits and manifestations of anomalous perceptions of the self. The fourth uncovers neural mechanisms of visual illusions and allows us to differentiate regions involved when a perceptual change is experienced in comparison to identity change (or depersonalization-like phenomenon). The last study nicely bands together resting state neural network correlates with schizotypy and the experience of ASEs.

Altogether, findings allow us to hypothesize a neuroimaging model showing that the state of ASE derives from personality traits of schizotypy. In the following discussion we will explain why the terms depersonalization and ASEs were used interchangeably and their link with schizotypy, we will then argue that ASEs and depersonalization could be considered as an expression of positive schizotypy. Then, more precisely we will open the debate on whether

schizotypy enhances the proneness or the persistence of ASEs. Furthermore, structural neural correlates will be discussed as characteristics of enduring traits, and functional correlates as sustaining transient states.

2.1 Depersonalization and anomalous experiences as expression of positive schizotypy?

In the present thesis the terms depersonalization-like phenomena and anomalous self-experiences were used to describe the same phenomenon triggered by the mirror gazing task. In studies 3, 4 and 5, the mirror gazing task seem to induce such phenomena as we could observe that some participants transiently lost their sense of self and experienced themselves as other facial identities. In this context we wish to open the discussion on these two concepts; depersonalization-like phenomena and anomalous self-experiences. Although we believe that these concepts can be differentiated in essence, they seem to share common characteristics. Sass and colleagues conducted a comparative investigation of anomalous self-experiences in depersonalization and schizophrenia (Sass et al., 2013). They recognized that depersonalization disorders (DPD) are characterized by analogous, although not identical, forms of ipseity (basic/minimal self) disturbances. The most striking example of a similarity between ASEs observed in DPD patients and in patients at risk for schizophrenia disorders assessed with the EASE, is that DPD patients described the mirror phenomenon as “If I look in the mirror, there is something different. Maybe it is just the eyes” and patients assessed with the EASE describe it as “when I looked at myself in the mirror, […] I felt that my face was changed”. Hence, the mirror phenomenon is described both in patients with DPD (Sierra, 2009) and in patients subjected to self-disturbances as described by the phenomenologists. In addition, Caputo (Caputo, 2019) investigated the link between dissociation phenomena as measured by the Clinician Administered Dissociative States Scale (CADDS, (Bremner et al., 1998)) and strange face illusions experienced during mirror-gazing. He highlighted that depersonalization factor

reflected illusions of lifeless body face, and illusions of living relatives, which agrees with our results from study 5 that evidences correlations between depersonalization-like strange face illusions and schizotypy in adolescents. This effect of depersonalization of strange-face illusions might be explained in terms of discontinuities in the integration of face representation into body self-representation, leading to transient loss of "mineness". In the self-referential processing model of Northoff (Northoff et al., 2006), depersonalization-like phenomena can be associated with the second ego-referential level of "minimal self". Hence, the features of depersonalization might be integrated in the concept of anomalous self-experiences defined by the phenomenologist as disturbances of the minimal self. The main difference between the two concept is that DPD patients as defined by the DSM are not schizophrenic, thus they are not expected to share all the subjective self-related features of schizophrenia spectrum disorders. However, in the context of the mirror gazing task, we hypothesize that we capture anomalous perceptual subjective experiences that could relate to both concepts as they present similar phenomenology.

In the below passage, we try to disentangle the relationship between the two concepts of depersonalization and anomalous self-experiences and the concept of schizotypy. In the existing literature, the terms psychotic experiences, schizotypal experiences, anomalous experiences and psychotic like experiences have been used interchangeably (Kwapil & Barrantes-Vidal, 2015). In addition, schizotypal experience has been defined as a dimension of unusual perceptual experiences, such as hallucinations varying on a continuum from extreme forms in patients, to lesser forms in typically developing individuals (Claridge & Beech, 1995). Hence, the differentiation between all these concepts is not clear, raising the question as to what may account for the shared characteristics and relationship between depersonalization, anomalous self-experiences and schizotypy?

In the field of self-disturbances in schizophrenia spectrum disorders, depersonalization constitutes a syndrome that encompasses feelings of detachment from one's self. A number of studies observed that dissociative symptoms (including depersonalization) significantly overlap with the tendency to report schizotypal traits (Merckelbach et al., 2000; Pope & Kwapil, 2000). Notably, Simeon and colleagues (Simeon, 2004) specifically investigated the relationship between depersonalization and positive schizotypy with the use of Perceptual Aberration Scale and Magical Ideation Scale, where they found higher scores on both schizotypy scales in DPD. However, Simeon and Hamilton (Simeon & Hamilton, 2008) highlighted an important phenomenological difference between depersonalization and schizotypy: that depersonalization is a disorder of self-perception but with an absence of cognitive difficulties. Reinforcing the link between ASEs and positive schizotypy, Debbané and colleagues (Debbané et al., 2014) suggested that neural correlates of self-reflective processes (medial prefrontal cortex and posterior cingulate cortex activations) associated with positive schizotypy might sustain diminished self-affection processes. This is why we hypothesize that the depersonalization, and thus what we also called ASEs, that we capture with the mirror gazing task might be the expression of positive schizotypy rather than overlapping constructs. In other words, what we might measure are some subtypes of unusual perceptual experiences related to the self when gazing in the mirror that would be an expression of the positive personality features of schizotypy. This hypothetical view could be further sustained by results of study 3 and 5. In study 5 we could observe that adolescents experiencing ASEs on the task presented higher levels of positive and disorganized schizotypy. However, in study 3 we could see that only the positive dimension of schizotypy could differentiate children and adolescents expressing ASEs, revealing the potential specificity of positive schizotypal features in this context.

2.2 Schizotypy enhances the proneness to ASEs? Or schizotypy heightens the persistence of ASEs?

Self-disturbances aggregate selectively in schizophrenia spectrum disorders, emerge during childhood and adolescence, and can be observed in individuals at-risk for psychosis. Moreover, a study investigated the prevalence of ASEs in a non-clinical group of individuals with high level of psychometrically defined schizotypy (Torbet et al., 2015), and showed that the latter group of individuals scored significantly higher on the EASE scale. However, we do not know whether schizotypy is related to ASEs in terms or proneness (as in presence of specific schizotypal features increase the proneness to self-disturbances), or whether schizotypal features are linked with the persistence of ASEs (as in ASEs change from a transient state to a recurrent one). Results from study 3 and 5 seem to be in accordance with the first hypothesis, as we could observe that children, adolescents and adults who experienced ASEs presented higher scores on the positive and disorganized dimensions of schizotypy. Furthermore, in study 3 we could observe that ASEs are expressed more frequently in adolescents when compared to children and adults and that the increased experience of ASEs during the transition from childhood to adolescence was sustained by positive schizotypy. We believe the core status of ASEs is inscribed in a certain temporality, as in a change of the structure of the core self-consciousness, but what if schizotypy enhances their recurrence, making them persistent over time in the long term? Here, we refer to the existing literature on psychotic like experiences (PLEs), hypothesizing that MGT-induced illusions would be at the potential nonclinical end of hallucinatory experiences continuum. The hypothesis for such development is that personality characteristics may play an important role in the appraisal and reaction to PLEs (Kline et al., 2012), therefore trait schizotypy could be seen as a moderator of the relationship between PLEs occurrence and persistence. In study 5 we found that disorganized schizotypy seemed to be

associated with the persistence after one year of atypical brain connectivity related to the ASE group within the default mode network. Similarly, in a study investing the link between PLEs and schizotypy, results showed a stronger association between PLEs and individuals with higher schizotypy traits when compared to their low-schizotypy peers (Kline et al., 2012). Future studies should investigate in high trait-schizotypy the more salient dimension of schizotypy to confirm the effect of disorganized schizotypy on ASEs, and might assess the quantity, frequency, intensity and persistence of these experiences in the long-term.

Another interesting study, conducted using Experience Sampling Method (ESM), investigated increased transfer of momentary mental states indexing anomalous self-experiences from one moment to the next (Wigman et al., 2013). At the momentary level, an initial anomalous experience may be updated over time by a more benign mental state, following interaction with external or internal representations. At each moment, the individual would 'test' the representation of the anomalous experience against his internal or external context. It would then be hypothesized that the level of persistence of momentary anomalous self-experience (in the case of the MGT) might be crucial to determine to which degree an individual may develop psychotic symptoms in interaction with the environment as well as with the level of vulnerability for expression of psychosis (schizotypy). In this context we are wondering whether the expression of vulnerability for psychotic symptoms (schizotypy) could moderate altered transfer of momentary mental states indexing anomalous self-perception (i.e. induced-ASEs or attenuated hallucinatory experiences). In Wigman's study (2013), they indeed showed that higher level of positive schizotypy prospectively predicted greater probability of persistence of momentary anomalous experiences over time in daily life.

Applicable to the context of this thesis, and in reference to study 3, we could hypothesize that a greater level of expression of positive schizotypy in healthy individuals might be associated with greater level of persistence of ASEs from one moment to the other. Furthermore, the

disorganization factor of schizotypy has been shown to influence the expression of positive schizotypy (Dominguez et al., 2010), and to significantly mediate the progression of positive schizotypy (Debbané et al., 2013). Hence why we could hypothesize that disorganized features of schizotypy when associated with positive features might heighten the proneness to ASEs. These considerations will be further discussed in terms of predictive coding model of apparitions of ASEs in a neuroimaging perspective below.

Although it is widely believed that mental disorders have their origin in altered cerebral structure and functions, the theoretical considerations exposed above do not map what the brain does in term of mediating the continuous flow of perceptions of the environment that guide adaptive behaviors. Therefore, after discussing the theoretical framework and the overlap between the different concepts, we go on with the neuroimaging information that we gathered and helped characterize further the relationship between schizotypy and ASEs.

2.3 Structural evidence for enduring traits: schizotypal features

Studies 1 and 2 focused on structural correlates of schizotypal features in a longitudinal manner, allowing us to identify the regions presenting atypical development in adolescents with higher schizotypal features. The aim of these studies was to investigate whether the personality trait of schizotypy was associated with brain structure in healthy individuals similarly to the pattern of atypical anatomy observed along the schizophrenia spectrum. In summarizing the literature, there is evidence for the critical period of adolescence as a transition in terms of structural changes to which could relate our findings. The involvement of the frontal lobe has been related to negative symptoms and cognitive impairments in schizophrenia (Sanz et al., 2009), similarly in study 1 we could relate atypical trajectories within the frontal lobe to the negative dimension of SPQ. The cingulate gyrus, is a part of the limbic system involved in

emotions and attention processing (Devinsky et al., 1995), and was associated to positive (posterior cingulate) and disorganized schizotypy (anterior cingulate) in our study. These regions were found abnormal along the schizophrenia spectrum (Haznedar et al., 2004), and notably the anterior part was associated with symptoms of disorganization (Liddle et al., 1992). In addition, atypical thalamic and pallidum volumes development were found in study 2, corroborating schizophrenia spectrum studies (Byne et al., 2001b;Hazlett et al., 1999). Hippocampus and lateral ventricle differential volumes were also identified in study 2 associated with disorganized schizotypy.

These 2 studies helped us answer one of our research questions: "How does schizotypy confer a risk for the development of high-risk states?". Based on the underlying neural correlates of schizotypy dimensions, we could uncover that negative features convey a potential risk-factor for later development of schizophrenia spectrum disorders. While when taking into account the continuum illusions-hallucinations, and with confirmation of study 3 and 5, the positive and disorganized features of schizotypy are potentially more related to the risk of developing the particular symptom of depersonalization. We chose to investigate structural correlates of schizotypal features because they are thought to be driven by genetic and maturational processes. These parameters reflect information about early brain development, which should be relatively stable during the lifespan. As a consequence, we believe these were the best indices to study enduring personality traits.

The investigation of cortical thickness and subcortical regions offers information on underlying stable differences in brain morphology and could represent a base from which to study the apparition of phenomena such as anomalous self-experiences. Indeed, researchers have suggested that the brain mechanisms underlying schizophrenia reflect dysfunction of brain networks, instead of abnormalities in particular brain regions (Williamson & Allman, 2012).

2.4 Functional evidence for transient states: attenuated unusual perceptual experiences of the self

Study 4 proposed a neurodynamic model following the course of a visual illusion as triggered by the MGT and resembling visual hallucination, from which we uncovered the mechanism of apparitions of visual illusions. In addition, study 5 evaluated resting state connectivity related to visual illusions. Our interest lies in the relationship between resting state and patterns of activations, as we believe both neural properties are involved in the mechanisms of apparitions of anomalous self-experiences.

There is evidence for structural correlates of hallucinatory behavior associated with abnormalities in the brain pathway of the sensory modality of the hallucination (Allen & Modinos, 2012), involving prefrontal, superior temporal and sensory regions. The structural evidence can be linked to models based on functional neuroimaging studies. The first model incorporates bottom-up and top-down processes involving multiple networks. The bottom-up processes include overactivation in sensory cortices resulting in increased anomalous perceptions, while top-down processes including regions such as the cingulate, prefrontal and premotor areas, are involved in cognitive/psychological mechanisms of hallucination formation. Finally, alterations in regions playing a role in regulation of emotions, such as parahippocampal gyri, cingulate, orbito-frontal and insula, may be involved in the affective/emotional characteristics of hallucinations. Examining hallucinatory experiences in the general population is beneficial to understand these network models. Therefore, in study 4, we could differentiate the regions involved in the transition between resting states and emergence (anterior insula and anterior cingulate cortex) - and these two regions seemed to be involved in the maintenance of the distinction self-other, ongoing (frontal, occipital cortices and insula) and off sates (DMN) of the illusions. Predictive coding (Horga et al., 2014; Sterzer et al., 2018) provided a general framework to minimize predictive errors when comparing the

anticipated signal with the actually occurring incoming stimulus. When an imbalance between anticipated predictions and actual sensory input is detected (such as when there is a mismatch due to the set-up of the MGT), the emphasis is put on the anticipated input, which results in an illusion. Furthermore, study 4 showed that an under activation of regions involved in maintenance of self-recognition (ACC and insula) led to anomalous perception of the self or depersonalization-like phenomena. Therefore, results from this thesis support the idea that deficient predictive coding may be a core pathophysiological mechanisms underlying psychotic symptoms (Fletcher & Frith, 2009), and sustained by alterations of activations in specific brain regions.

Another conceptual framework of hallucination theory (Northoff & Qin, 2011) proposed (in their case for auditory verbal hallucinations) that resting state activity prior to the hallucination enables and predisposes the brain to hallucinatory experiences, providing an explanation for the initial activation of sensory regions (bottom up). This model postulated abnormal resting sate activity in the sensory cortex and abnormal modulation of the DMN. In line with this hypothesis, we observed in study 5, differential resting state connectivity within the primary visual network and DMN of adolescents experiencing induced-ASEs (depersonalization-like phenomena).

With this in mind, by linking study 4 and 5, we could hypothesize that atypical connectivity in resting state networks observed in our adolescents predisposes their brain to later experiences of anomalous visual illusions when performing the task. Providing already an 'atypical endogenous baseline', which when under stimulated by the set-up of the MGT, triggers the cascade of bottom up and top down mismatch evolving in ASE-like experiences. Clinically, the underlying mechanisms of apparitions of ASEs would represent potential targets for preventive interventions and could prevent the clinical pathology to develop.

2.5 The state derives from the trait: evidence from neuroimaging studies

We believe, that pathology of schizophrenia is known to involve both early and enduring neurocognitive vulnerability (Jablensky et al., 2017), as well as later developments of responses to endogenous factors and challenging life events. Structural correlates of the brain should be at the basis of functional activity; however, linking the two remains challenging.

The hypothesis is that the anatomical architecture determines, but not strictly, the network dynamics (Honey et al., 2007). The brain can be considered as the most complex system, with various interactions between structural and functional organizations. These elements in turn are continuously updated depending on the sensory incoming information and the feedback that emerge, resulting in a functional and adaptive remodeling at different organizational systems. Which poses the question: under what conditions favorable plastic responses happen to be aberrant and therefore expression of maladaptation?

Altogether, gathering results from the different studies included in this thesis, we developed an integrative model, including brain measures, enduring personality traits and anomalous self-experience phenomena, see figure 24. We believe that the latent structure of the brain and its remodeling during adolescence (with synaptic pruning and myelination) condition personality, notably schizotypal personality traits. This structural organization is closely related to the functional topology reflected by the organization of resting state networks; thus, this topology might be modulated by personality traits and their evolution throughout development. If we consider the case of anomalous self-experiences, we could hypothesize that positive personality traits influenced the baseline topology of resting state networks which are atypically organized when compared to adolescents who do not experience ASEs. Subsequently, when we trigger the apparition of visual illusions, adolescents with higher enduring positive schizotypal traits, who presented an atypical resting state baseline, would be more prone to experience anomalous self-experiences. In line with this, they would then present atypical activations of regions

responsible for the distinction self-other, which would lead to the experience of one's self as another identity.

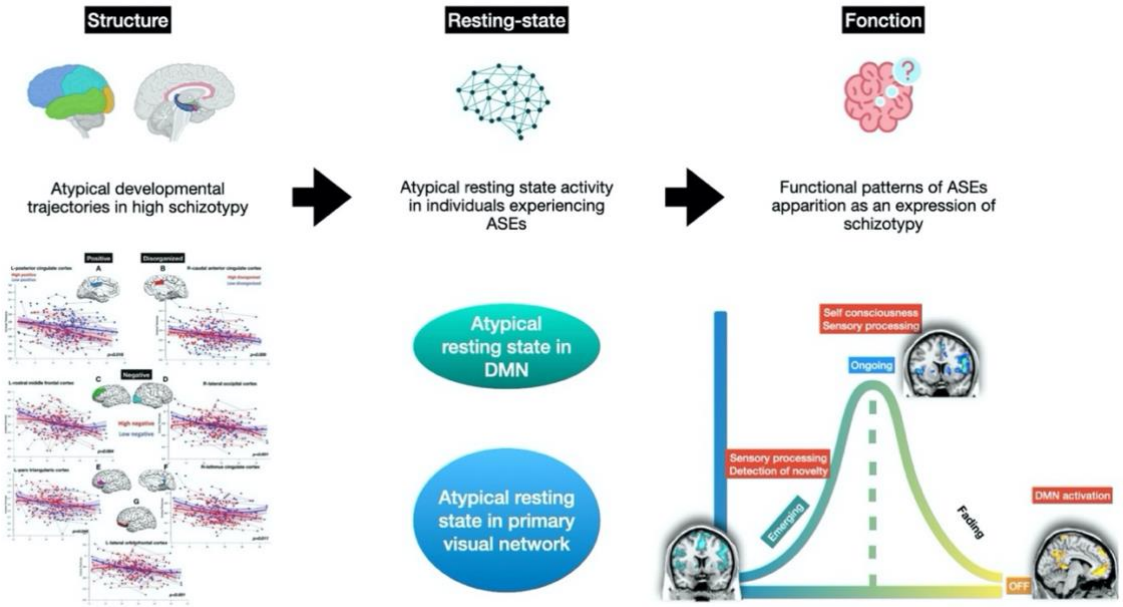


Figure 24: The state derives from the trait – neuroimaging evidence

Schema summarizing findings from the different studies and showing the link between them.

3. Limitations and further directions

This section discusses the limitations of the studies. Some have been discussed previously, in particular limitations related to sample size, software use and validity of findings were assessed in the empirical section and included in the discussion of each studies. Hence, in the next paragraphs we will discuss general limitations of the present thesis.

3.1 The measure of schizotypy during adolescence

Heightened expression of schizotypal features is usually observed during adolescence, where typical development as well as emergence of psychopathologies can cloud the general picture. The sole use of psychometric measures of schizotypy is a limitation for the study, what we called 'high schizotypy' was a relative measure under the influence of the sample recruited. Therefore, this term is to interpret with caution. An idea would have been to screen 'true' high schizotypes from the general population using interview-based assessments. This type of measurement is suggested to be more sensitive in selecting groups with cognitive impairments related to schizotypy (Bedweel et al., 2009). A use of both self-report and interview-based is preconized for future research.

3.2 Examining the full range of schizotypes

The recruitment of participant was made in the community; therefore, our participants only represent relative high scorers on the different dimensions. It was proposed that only neuroschizotypes would be related to clinical disorders, and thus share similar phenotypes. Hence, it would have been of interest to recruit participants constituting this subtype. It would have benefitted the present work to include markers of abnormal development related to neurological soft signs, for instance those that are present in schizotypal samples.

3.3 Multidimensional structure of schizotypy

Although the three-factor model of schizotypy is the most supported consensus, other dimensions have been hypothesized, including a separate impulsive-non conformity factor (Mason et al., 1995) and paranoia factor (Horton et al., 2014). In parallel, the idea of studying schizotypy as clusters instead of individual dimensions came up, showing that negative cluster was associated with executive functions deficits, while clustering both high positive and negative schizotypy was associated with unusual social behaviors (Suhr & Spitznagel, 2001). In another study, it was observed that clusters predicted more efficiently neurological 'soft signs' than when using dimensions (Barrantes-Vidal et al., 2003). An alternative to the present study would have been to use this cluster classification instead of each dimension individually.

3.4 High risk models

The link between schizotypy and the state of ASEs is sustained by the hypothesis that we recreate a high-risk state with the MGT. This observation relies on the validity of the theoretical construct of schizotypy and the assumption of high-risk models of psychosis that subclinical forms of psychosis symptomatology are shared between high schizotypal individuals and clinical high-risk patients. Whilst high-risk model is an emergent popular concept, it is also criticized (Lawrie et al., 2010).

3.5 Measure of anomalous self-experiences

In the phenomenological theories, ASEs are considered as trait-like disturbances of a person's experience of themselves, also named 'trait phenomenon' (Parnas & Henriksen, 2014). These findings were supported by Raballo and colleagues, who observed that schizophrenia and schizotypal personality disorders patients shared comparable level of non-psychotic experiential anomalies, confirming self-disturbances as potential phenotypes for schizophrenia

spectrum (Raballo, Saebye, et al., 2011). We could not directly test the 'trait-like' dimension in our studies. In their literature Parnas, Sass, Raballo and colleagues developed and mostly use the EASE to measure the trait-like features of ASEs in everyday life using interview-based measures, whereas we created a task inducing ASEs as very temporary in the general population. Thus, in the present work we considered induced-ASEs as pure state phenomena. The nature of ASEs would have greatly benefit from further investigation of the link between state-ASEs as induced with the mirror-gazing task and trait-ASEs as defined with the EASE.

3.6 Diminished self-affection and depersonalization

In phenomenology, diminished self-affection relates to both anomalous self-experiences and depersonalization, and it is described as a reduction in the very sense of existing as a subject, as a first-person perspective on the world (Sass et al., 2013). Depersonalization also includes attenuation of self-presence (existing as a subject of experience) that relate to a diminished sense of agency. In the present thesis, we focused on an aspect of depersonalization mostly related to illusory sensory phenomenon, and we could find that such phenomena were mostly related to positive schizotypy. However, as negative symptoms of schizophrenia have been found to relate to affective deficits, we could hypothesize that the aspect of self-affection might be associated with negative schizotypy (Cohen & Matthews, 2010). Hence, further studies should consider this other aspect of depersonalization and investigate the link with schizotypy. We could think of a way of inducing this aspect within the mirror gazing task, to do so we would need to trigger participants to identify themselves to their perception, and to lose their sense of self during the task. The mirror gazing task could be upgraded with some aspects of the enfacement illusion task (Tsakiris, 2008), which reported that multisensory integration can induce a bias in self recognition towards recognition of the other person, and update cognitive representation of one's representation of the self, such as the sense of ownership.

3.7 The power of suggestion

Terhune and Smith investigated the variables involved in the induction of mirror-gazing hallucinations, focusing on the role of suggestion (Terhune & Smith, 2006). Participants who were allocated to the 'suggestion' condition reported significantly more visual apparitions than those who were in the control condition. Thus, although the mirror gazing task is an efficient procedure to induce visual illusions, the presentation of suggestion before the task could influence the frequency of apparitions. Whilst we tried to remain as neutral as possible when giving instructions before the task "you may or may not perceive a change", there is still a non-negligible subtle suggestion when we say, "if you perceive a change, press the button […]". Moreover, participants did not have information concerning the mirror-gazing task prior to participation, as it is known that volunteering for studies on sensory deprivation and prior knowledge influence the phenomena experienced in the experimental setting. Future study using the MGT should firstly confirm the effects of suggestion and prior knowledge, and subsequently control for their eventual effect.

3.8 The effect of other confounding factors

Although we included a number of covariates in the studies conducted (gender, age, IQ, internalized and externalized behaviors), other confounding factors could play a role in the results obtained. Firstly, cannabis consumption is known to interact with the levels of schizotypy, notably during adolescence. Cannabis use plays a role in the development of schizophrenia in young adults, but prior to age 14 it also predicted symptoms of schizotypal personality disorders in adulthood (Anglin et al., 2012). Secondly, childhood trauma has been shown to have an effect on schizotypy and dissociation phenomena. A review identified that studies supported the association between trauma and schizotypy, more specifically, individuals who reported adverse experiences in childhood scored significantly higher on

positive and negative schizotypy (Velikonja et al., 2015). Moreover, traumatic childhood experiences were found to engender dissociative symptoms later in life, notably emotional and physical abuse as well as emotional neglect correlated significantly with Dissociative experiences Scales scores (Watson et al., 2006). Thus, this thesis would have greatly beneficiated from inclusion of measures of such confounding factors.

3.9 The healthy side of positive schizotypy

As mentioned in the introduction, individuals clustered with high positive schizotypy features might represent happy schizotypes and tend to display less impairments than others clustered with high negative features. The positive cluster was associated with adapted traits related to openness to experiences, extraversion, creativity and flexible/unconventional thinking (Mohr & Claridge, 2015). This implies that further studies should consider including measures of such features (creativity scale, assessment of the Big Five), in order to differentiate happy schizotypes from other clusters.

3.10 Methodological limitations

Information collected from participants on their family history lacked details. It would have been informative to collect more of this information, which would provide an insight into the extent of schizotypal features in relation to genetic proximity. It would bring a new dimension in term of classification on the presence of family history or not.

Precise limitations to the use of software and analyses have been presented in each study. In general, the use of multiple neuroimaging assessment represents a strength of the study, however, we did not have a direct comparison of the different techniques. A multimodal

integration would greatly benefit the understanding of the link between structural and functional imaging.

4. Clinical implications and future perspectives

A number of areas could be considered for future research. First, replication of the mirror gazing task methodology both behaviorally and with fMRI in schizophrenia spectrum clinical population, such as patients at high risk for psychosis would consolidate our findings and validate our hypotheses. In addition, replication in other disorders (borderline disorders, depersonalization disorders or depression) would bring to the table similarities and differences with what is observed along psychotic disorders. Whether induced anomalous self-experiences are specific to psychotic disorders could reintegrate the importance of the self in the DSM and the importance of personality in phenomenology.

In addition, if replicated the MGT could provide a non-invasive experimental diagnostic test for subjective disturbances of the self that could be detected way before the onset of psychosis and would complete interview questionnaires such as the EASE in which symptoms are only self-reported. Furthermore, in this thesis we built upon the premises of minimal self-disturbances, it would then be interesting to investigate these disturbances in a trait-state approach. A future study could for instance ally interview-based assessment such as the EASE, which would be considered as trait-ASEs, and ASEs states as induced with the MGT.

Furthermore, a critical review from Motillon and colleagues (Motillon et al., 2018), proposed new perspectives for therapeutic use of the mirror, which could help schizophrenia patients to improve self-other differentiation. Thirioux and colleagues developed a paradigm, “the double mirror”, in which they could manipulate the self-face identification so they could study disturbances of self-consciousness in schizophrenia (Thirioux et al., 2016). Hence, following

these ideas, the mirror gazing task could provide groundwork for cognitive remediation and could be used to this effect in clinical populations.

Finally, building upon our neural model of apparition of ASEs, an option would be to use real time fMRI, notably fMRI-neurofeedback training on brain regions involved in the emergence of visual hallucinations. Training with neurofeedback population at risk for psychosis could help prevent the emergence of hallucination, and the transition to full-blown psychosis.

5. General conclusion

The five studies included in this thesis have investigated the characteristics of two aspects of early detection of psychosis. In view of this, two studies further broaden the knowledge on trait schizotypy, notably in terms of neurobiological correlates, whereas the other 3 studies looked into phenomena of depersonalization-like states and anomalous self-experiences. The overarching goal of these linked studies was to understand the link between the two trait and state aspect before the onset of psychotic disorders.

Schizotypal traits were found to share brain structural characteristics with the spectrum of psychotic disorders. And negative features were highlighted as conveying the predictive value of the risk to develop psychotic disorders later in life, while positive and disorganized features were associated with interindividual differences linked to personality.

Looking at one's self in the mirror is one of the strongest phenomenological experience of the self, requiring identification of the specular image as belonging to the individual. Hence, the 3 last studies have employed the mirror gazing task to induce experiences of anomalous self-experiences, resembling phenomena of depersonalization. Positive features were found to increase the propensity to experience depersonalization-like phenomena during the period of transition from childhood to adolescence and disorganized features were argued to mediate the progression of positive features.

Altogether, neuroimaging evidence allowed us to establish that the state derived from the trait. The latent structure of enduring traits was hypothesized to modulate the baseline functional topology of resting state networks, thus, when illusory phenomena were triggered by the mirror

gazing task, atypical network organization would translate into atypical activations of regions implicated in the distinction self-other, leading to experiences of one's self as another identity.

This thesis provides a needed clarification of the neural correlates of schizotypal features, it allows for reconciliation between the contemporary concept of schizotypy and the dimension of Self as an important characteristic in the early stage of the continuum of psychotic disorders. Furthermore, uncovering the mechanisms of apparitions of perceptual disturbances provides a framework for decoding pathological hallucinations patterns, which could benefit research on drug-resistant hallucinations. Altogether the present work carries the potential to inform future innovative detection of early psychosis and treatment such as fMRI-based treatment (neurofeedback) and cognitive remediation.

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Appendix 1.

SPQ questionnaire

SPQ

A. Raine, traduit par P. Dumas, F. Rosenfeld et T. d'Amato

Nom du participant _____ Date actuelle _____ Date de naissance _____

Questionnaire remplis par : ☐ participant ☐ mère ☐ père ☐ mère & père Autre _____

Il est important de le remplir entièrement, même si plusieurs questions paraissent très éloignées de vos préoccupations ou si vous trouvez que plusieurs d'entre elles se ressemblent.

Nous avons bien conscience que certaines réponses peuvent varier en fonction du contexte (par exemple si vous êtes en famille, avec des amis ou au travail) ; dans ce cas, il faut se représenter une situation « moyenne » en se posant la question : « au fond, est-ce que, en général, je pense plutôt comme ceci ou comme cela ? ».

	Oui	Non
1. Il m'arrive d'avoir l'impression que ce que je vois à la télévision ou ce que je lis dans les journaux m'est personnellement destiné.	☐	☐
2. Il m'arrive d'éviter les lieux où il y a de la foule, car j'y deviens facilement anxieux.	☐	☐
3. J'ai déjà eu des expériences en rapport avec des choses surnaturelles.	☐	☐
4. Il peut m'arriver de prendre des ombres ou certains objets pour des personnes ; ou bien certains bruits pour des voix.	☐	☐
5. Je pense que beaucoup de gens me considèrent comme quelqu'un d'un peu bizarre ou un peu curieux.	☐	☐
6. Je trouve peu d'intérêt à faire la connaissance d'autres personnes.	☐	☐
7. Les gens ont parfois du mal à comprendre ce que je dis quand je me lance dans une explication.	☐	☐
8. Les gens me trouvent parfois lointain ou distant.	☐	☐
9. J'ai le sentiment qu'on parle de moi dans mon dos.	☐	☐
10. Je me rends compte que les gens me remarquent quand je sors pour aller au restaurant ou au cinéma.	☐	☐
11. Je deviens facilement très nerveux quand je suis obligé de tenir des conversations de courtoisie avec les gens.	☐	☐
12. Je pense que certaines personnes ont le don de télépathie (lecture de la pensée des autres).	☐	☐
13. Il m'est déjà arrivé d'avoir la sensation de sentir une force ou une présence auprès de moi, alors même que j'étais tout seul à ce moment-là.	☐	☐
14. Les gens font parfois des commentaires sur mes comportements ou certaines de mes manières qu'ils trouvent inhabituelles.	☐	☐
15. En général, j'aime mieux garder pour moi ce que je pense.	☐	☐
16. Je saute parfois du coq-à-l'âne quand je discute.	☐	☐
17. J'ai du mal à exprimer mes véritables sentiments, que ce soit au moyen de la parole ou avec le regard.	☐	☐
18. J'ai souvent le sentiment que les gens ont de mauvaises intentions à mon égard.	☐	☐
19. Il arrive que les gens me fassent des allusions voilées ou disent des choses à double sens.	☐	☐
20. Ça me rend nerveux de sentir quelqu'un marcher derrière moi.	☐	☐
21. Je suis parfois convaincu que d'autres personnes seraient capables de dire ce que je suis en train de penser.	☐	☐

		Oui	Non
22.	Quand je me regarde dans un miroir ou quand je regarde quelqu'un d'autre dans un miroir, il m'arrive d'avoir l'impression de voir le visage se modifier légèrement.	☐	☐
23.	Il arrive parfois que les gens pensent que je suis un peu étrange.	☐	☐
24.	La plupart du temps je reste silencieux quand je suis avec d'autres personnes.	☐	☐
25.	Il m'arrive quelquefois de perdre le fil de ce que je suis en train de dire.	☐	☐
26.	Je ris et je souris rarement.	☐	☐
27.	J'ai parfois le sentiment que mes amis ou mes collègues de travail ne sont pas vraiment loyaux ou dignes de foi.	☐	☐
28.	J'ai déjà remarqué que certains objets ou certaines situations apparemment sans importance peuvent être des sortes de messages si l'on arrive à les décrypter.	☐	☐
29.	Je suis facilement anxieux quand je rencontre des gens pour la première fois.	☐	☐
30.	Je pense que la clairvoyance est un don que possèdent certaines personnes (parapsychologie, connaissance de l'avenir ou autre…).	☐	☐
31.	Il m'est parfois arrivé d'entendre une voix intérieure qui disait ou commentait mes pensées tout haut.	☐	☐
32.	Certaines personnes pensent que je suis quelqu'un de très bizarre.	☐	☐
33.	Ça m'est souvent difficile de me sentir proche des gens sur le plan émotionnel.	☐	☐
34.	Il m'arrive souvent de partir dans tous les sens quand je parle de quelque chose.	☐	☐
35.	J'ai du mal à utiliser les expressions du visage ou les gestes des mains pour communiquer avec les gens.	☐	☐
36.	Je sens que je dois rester sur mes gardes même avec mes amis.	☐	☐
37.	Il m'arrive parfois de voir des signes précis dans les publicités, les enseignes ou les vitrines de la rue, ou dans la façon dont les objets sont agencés autour de moi.	☐	☐
38.	Je me sens souvent nerveux quand je me trouve dans un groupe de gens que je ne connais pas.	☐	☐
39.	J'ai parfois le sentiment que d'autres personnes peuvent ressentir mes sentiments tout en étant loin de moi.	☐	☐
40.	Il me semble avoir déjà vu certaines choses que les autres ne pouvaient pas voir.	☐	☐
41.	J'ai le sentiment de n'être vraiment proche de personne en dehors de ma famille ou de mon conjoint ; ou qu'il n'y a pas vraiment quelqu'un à qui je puisse me confier ou parler de mes problèmes personnels.	☐	☐
42.	Certains me trouvent parfois vague ou peu clair lors des conversations.	☐	☐
43.	J'ai du mal à répondre aux invitations ou à rendre les politesses aux gens.	☐	☐
44.	Je relève souvent des remarques dépréciatives ou des menaces cachées dans ce que les gens disent ou font.	☐	☐
45.	Lorsque je fais mes courses, j'ai le sentiment que les gens me remarquent.	☐	☐
46.	Je me sens très mal à l'aise dans les situations où je suis en présence de gens que je ne connais pas.	☐	☐
47.	J'ai déjà eu des expériences particulières en rapport avec l'astrologie, la divination, le contact avec d'autres êtres, les perceptions extra-sensorielles, ou tout simplement j'ai le sentiment d'avoir un sixième sens.	☐	☐

		Oui	Non
48.	Il arrive que les objets qui m'entourent paraissent parfois inhabituellement trop grands ou trop petits, comme si leurs proportions avaient changé.	☐	☐
49.	Ecrire une lettre à un ami est si compliqué que cela n'en vaut souvent pas la peine.	☐	☐
50.	Il m'arrive d'utiliser les mots de travers.	☐	☐
51.	J'ai tendance à éviter de regarder les gens dans les yeux quand je leur parle.	☐	☐
52.	Je pense qu'il vaut mieux que les gens n'en sachent pas trop sur moi.	☐	☐
53.	Lorsque je vois des gens parler entre eux, je me demande souvent s'ils ne parlent pas de moi.	☐	☐
54.	Je serais très angoissé si je devais faire un discours devant un grand groupe de gens.	☐	☐
55.	J'ai déjà eu l'impression de parvenir à communiquer avec d'autres personnes rien que par la pensée.	☐	☐
56.	Il arrive que mon odorat devienne parfois inhabituellement développé.	☐	☐
57.	J'ai tendance à me tenir en retrait dans les situations sociales.	☐	☐
58.	J'ai tendance à m'écarter du sujet pendant une conversation.	☐	☐
59.	J'ai souvent l'impression que les autres ont quelque chose contre moi.	☐	☐
60.	J'ai parfois l'impression que les autres me dévisagent.	☐	☐
61.	Il m'arrive d'être subitement distrait par des sons lointains auxquels je n'accorde normalement aucune attention.	☐	☐
62.	J'attache peu d'importance au fait d'avoir des amis proches.	☐	☐
63.	J'ai parfois le sentiment que les gens parlent de moi.	☐	☐
64.	Mes pensées sont parfois si intenses que je peux presque les entendre.	☐	☐
65.	Je dois souvent rester vigilant pour que les gens n'abusent pas de ma confiance ou de ma bonne volonté.	☐	☐
66.	J'ai le sentiment qu'il ne m'est pas possible d'être proche des gens.	☐	☐
67.	Je suis quelqu'un d'original ou d'assez spécial ; en tout cas assez différent des autres.	☐	☐
68.	Ma manière de m'exprimer n'est pas très expressive et vivante.	☐	☐
69.	Je trouve qu'il est difficile de communiquer clairement aux autres ce que j'ai envie de leur dire.	☐	☐
70.	J'ai quelques habitudes excentriques.	☐	☐
71.	Je me sens très mal à l'aise quand je parle à des gens que je ne connais pas bien.	☐	☐
72.	On me fait parfois la remarque que mes propos sont embrouillés.	☐	☐
73.	J'ai tendance à garder mes sentiments pour moi.	☐	☐
74.	Les gens m'évitent parfois à cause de mon apparence excentrique.	☐	☐

Appendix 2.

Questionnaire post mirror gazing task

1a) Combien de fois avez-vous repéré quelque chose d'étrange ?

☐ jamais ☐ quelques fois ☐ souvent ☐ très souvent ☐ tout le temps

1b) Combien de fois cela vous a –t-il paru réel ?

☐ jamais ☐ quelques fois ☐ souvent ☐ très souvent ☐ tout le temps

1c) À quelle fréquence vous avez pensé que c'était une autre personne ?

☐ jamais ☐ quelques fois ☐ souvent ☐ très souvent ☐ tout le temps

2) Qu'est ce que vous avez-vu ? (énumérez ce que vous avez vu)

_____

_____

_____

3) Le changement était-il fixe, en mouvement, ou les deux ? _____

4a) Combien de temps avez-vous eu l'impression que l'expérience a duré ? _____min.

4b) ☐ 0-4 min. ☐ 4-8 min. ☐ 8-12 min. ☐ 12-16 min. ☐ plus de 16 min.

5a) Combien de fois avez-vous eu l'impression : de perde le contrôle

☐ jamais ☐ quelques fois ☐ souvent ☐ très souvent ☐ tout le temps

5b) de reprendre le contrôle

☐ jamais ☐ quelques fois ☐ souvent ☐ très souvent ☐ tout le temps

6) Avez-vous remarqué un changement particulier dans la couleur, la lumière ou le contraste ? Si oui, décrivez : _____

7) Avez-vous remarqué un mouvement particulier ? Si oui, décrivez :

_____

8) Avez-vous remarqué quelque chose de particulier au niveau de vos yeux ? Si oui, décrivez :

_____

9) Avez-vous vu une autre personne ? Si oui, décrivez :

_____

10) Avez-vous ressenti une ou des sensations corporelles pendant la tâche ? Si oui, décrivez :

_____

11) Avez-vous remarqué un bruit particulier ? _____

12) Avez-vous senti la présence de quelqu'un (autre que vous-même et l'expérimentateur au cours de la tâche ? Si oui, décrivez :

_____

Appendix 3.

Supplementary material – Study 1

1. Exclusion criteria

Exclusion criteria included: acute psychotic phase, and estimated performance on the Block Design and Vocabulary subtest below 1 std.dev of the developmental norm (based on the Cubes subtest of the Weschler Scales of Intelligence for children (WISC-IV)[1] or for participants older than 18 y.o, the Wechsler Adult Intelligence Scale[2] (WAIS-IV)). We had to exclude three participants because they did not have Vocabulary subtest data available. There was no MINI screening but a screening was made through medical questionnaire asking for any previous psychiatric diagnosis, treatment, epilepsy, and neurological disorders. On this basis we excluded from the present study: 7 participants who suffered from diagnosed anxiety disorders and depression, 5 out of 7 were following psychopharmacological medication, notably for depressive symptoms (Cytralex and Sertraline). 4 other participants were diagnosed for ADHD and all of them were on medication (Concerta or Ritaline). One presented schizoaffective disorder combined with a neurological disorder and was thus also excluded from the sample. None of our participants had experienced epilepsy.

2. Ethnicity of the adolescents and socio-economic description of their parents

Ethnicity

	1 = Suisse	2 = French	3 = Southern Europe	4 = North Africa	5 = South Africa	6 = Asia	7 = Mixed	8 = Others	Missing data
N	35	9	7	0	3	0	29	13	15

Parents's Socio-economic status									
Proffesional category	1 = Dirigeants, senior executive ..	2 = Academic and scientific professions	3 = Intermediate professions	4 = Administrative employés	5 = Customer service and sales personnel	6 = Farmers, hunters …	7 = Machine and industrial robots operators, crane operators, drivers … engib	8 = Workers and unskilled workers	Missing data
N	18	20	26	17	14	5	9	0	2
Formation level	1 = University & higher education	2 =Superior Proffesional schools	3 = A level	4 = Vocational school	5 = Apprenticeship	6 = compulsory school	7 =Less than compulsory school	8 = other	Missing data
N	56	4	9	4	19	15	2	0	2

Table1: Table representing the ethnicity of participants and the socio-economic description of their parents.

3. Psychological measures

Adaptive behaviors were assessed using the Youth self-reported questionnaire[3] (YSR) and, for participants of 18 y.o and older, with the Adult Self Report questionnaire[4] (ASR), yielding

internalization (withdrawal, anxiety, depression, and somatic complaints) and externalization (attention problems, aggressive behaviors and delinquency) problem scores. These scores were used as covariates in the analyses to more effectively isolate the effect of schizotypy.

Schizotypal personality traits were assessed with a validated[5] French version of the SPQ[6]. It consists of a 74-item self-report questionnaire based on the nine DSM-IV criteria for schizotypal personality disorder. The positive dimension combines the subscales: ideas of reference, odd beliefs or magical thinking, unusual perceptual experiences, and suspiciousness. The negative dimension includes constricted affect, excessive social anxiety, and having no close friends. The disorganized schizotypy comprises odd or eccentric behavior, and odd speech.

4. Distribution of raw SPQ scores per dimensions

The Y-axis represents the raw scores on SPQ. The X-axis represents participants ID's.

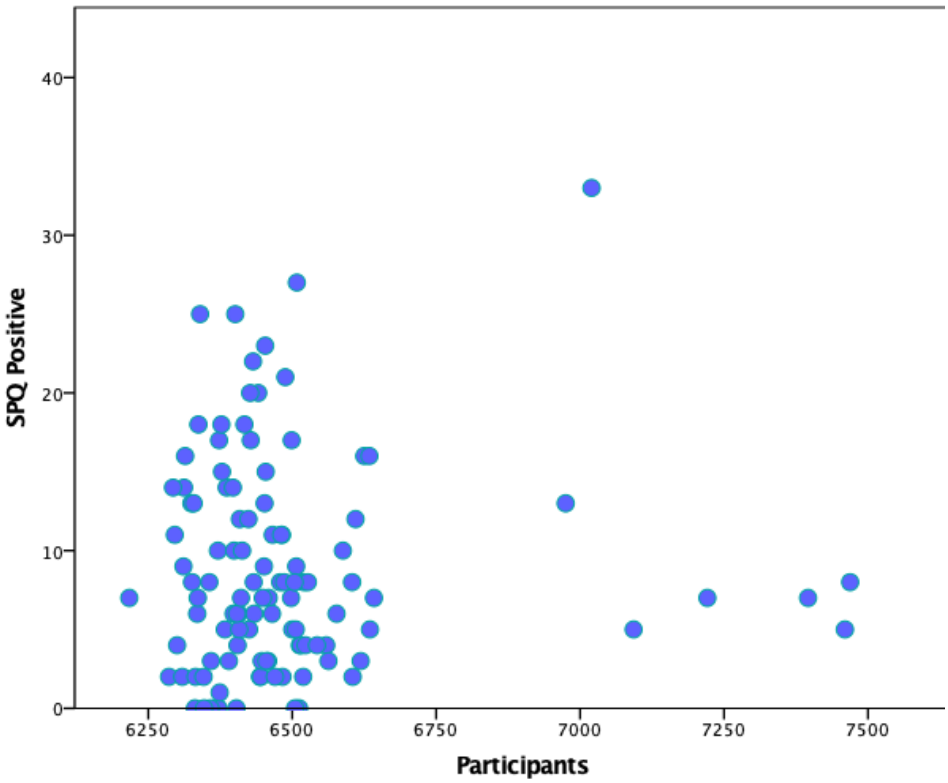

Figure 1: Distribution of the participants' raw score on the positive dimension

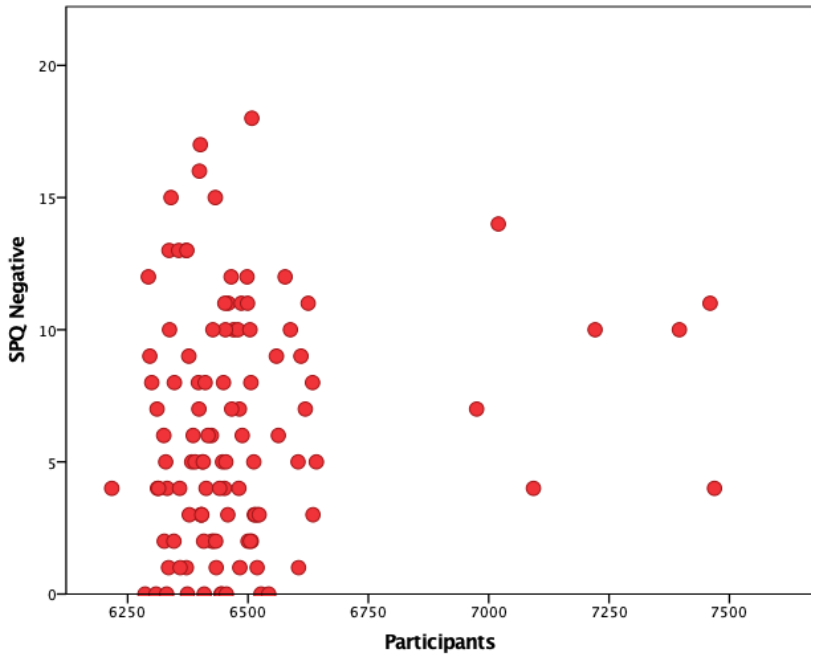

Figure 2: Distribution of the participants' raw score on the negative dimension

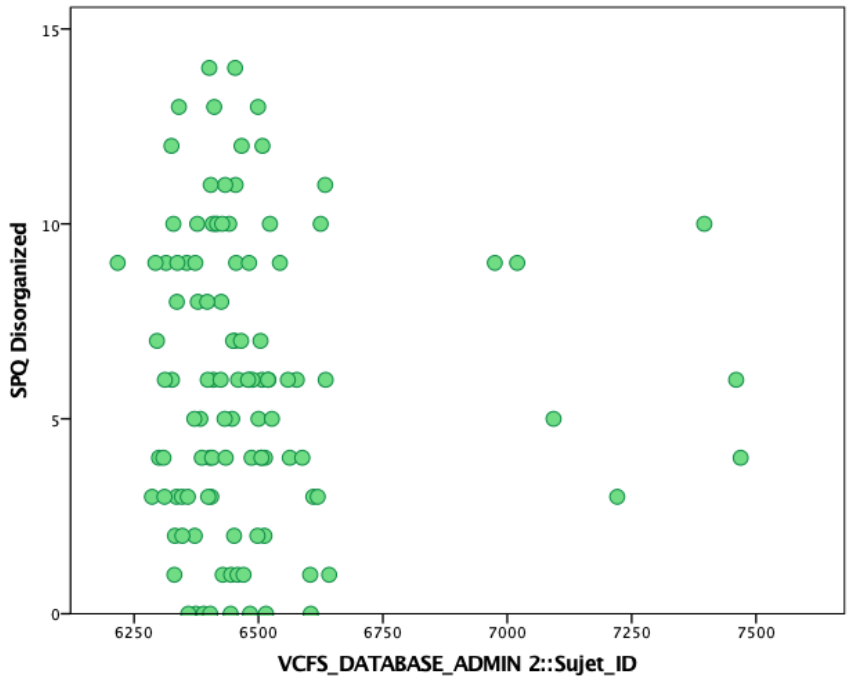

Figure 3: Distribution of the participants' raw score on the disorganized dimension

5. Justification of the use of Block Design as a covariate

Some facets of IQ were shown to be compromised along the schizophrenia spectrum, as well as in non-clinical schizotypy[7,8]. These studies exhibit the link between general IQ and schizotypy levels. Therefore, in our studies we wanted to include IQ as a covariate.

However, during the collection of data along the five years, we missed numerous data on the different subtests. The most consistent subtests available were the Block Design and Vocabulary subtests. Therefore, we included an average of Block design and Vocabulary scores as a measure of intellectual functioning. Among the different subtests, the Block Design and vocabulary test are the ones that account for the most variance (Sumiyoshi[9] et al (2013)). Moreover, when looking at a general factor (g) defined by 11 subtests, Blaha and colleagues[10] showed that the vocabulary test contributes most to the Full Scale Intelligent Quotient (FSIQ) and Block Design load for 0.71 on this mean g factor. In conclusion, we cannot say that block design and vocabulary represent a proxy measure of IQ, however, we included them as measures of intellectual functioning.

6. Procedure followed for cluster analyses

All procedure followed for cluster analyses were conducted in R.

6.1 Univariate Analyses – Within dimensions:

We performed univariate analyses for each dimension (positive, negative, disorganized) separately. For each dimension: rows represented participants (n=109) and the unique column represented the raw scores per participants on the dimension studied. There were no missing values and data was standardized.

For the univariate analyses we used optimal K-means clustering in One-dimension by dynamic programming (the package: Ckmeans.1d.dp) implemented in R. This function performs optimal k-means clustering on one-dimensional data.

In contrast to the heuristic k-means algorithms implemented for 3D data, this function assigns element in numeric vector into a number of clusters by dynamic programming[10]. It minimizes the sum of squares of within-cluster distances from each element to its corresponding cluster centre. When a range is provided for k (we gave a range from 1 to 10 clusters), the exact number of clusters is determined by Bayesian information criterion. A resulting efficient number of 2 clusters per dimensions was returned for each analysis.

As a validation of the clustering solutions we computed elbow and calinski-harabaz methods and displayed their visualisation.

The Elbow method looks at the percentage of variance explained when we increase the number of clusters, one should choose a number of clusters so that adding another cluster does not improve much better the variance explained. Visually, the location of a bend (knee) in the plot is generally considered as an indicator of the appropriate number of clusters.

The Calinski-Harabasz index is based on a ratio of between cluster scatter matrix and within cluster scatter matrix. A maximum value for CH indicates a suitable partition for the data set.

Below are presented the estimation of number of clusters as determined by BIC using the Ckmeans.1d.1dp function, the repartition into clusters for each dimension as well as the validity measures obtained.

For each dimension we looked at both methods (elbow and C-H). The elbow method for each dimension suggest 2 clusters, as a third cluster forms no elbow and thus provides no significant added value. When looking at the Calinski-Harabasz index, we can see that the third cluster is only slightly higher. From this we conclude that for each dimension the 2 cluster-solution is optimal.

SPQ Disorganized dimension

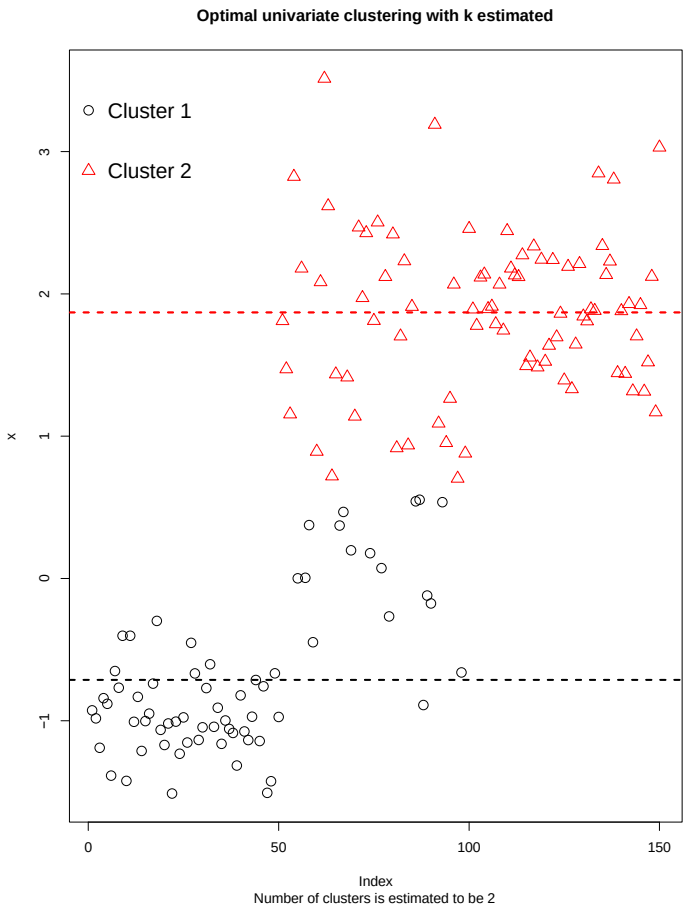

Figure 4: Two clusters were obtained from applying the ckmeans.1d.dp function on x= SPQ disorganized scores sampled from a Gaussian mixture model estimated with two components. The horizontal axis represents the index number of each point in the data. The dotted lines represent the centers of each cluster.

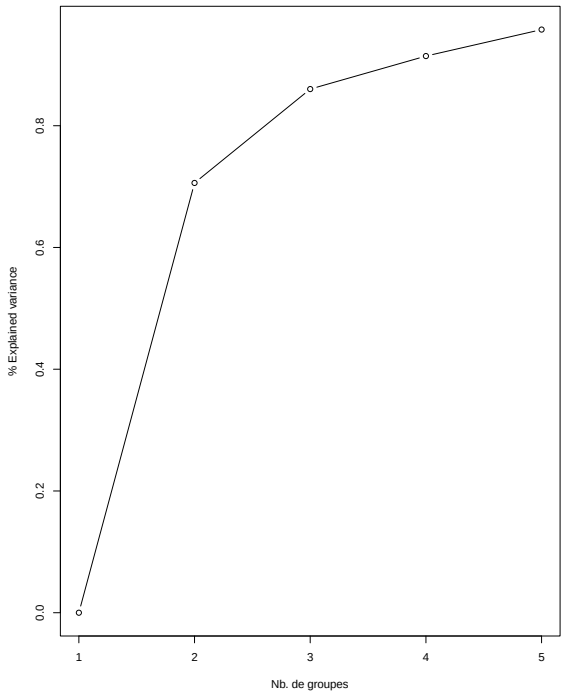

Figure 5: Elbow method for 2-solution cluster validation.

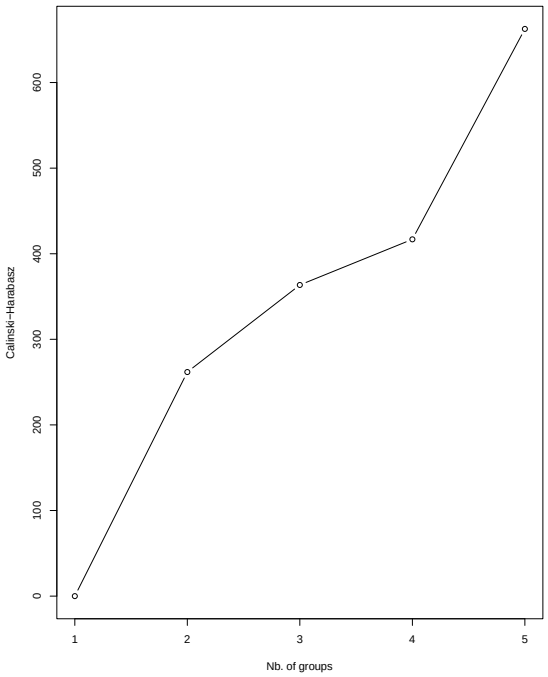

Figure 6: Calinski-Harabasz method for 2-solution cluster validation.

SPQ Positive dimension

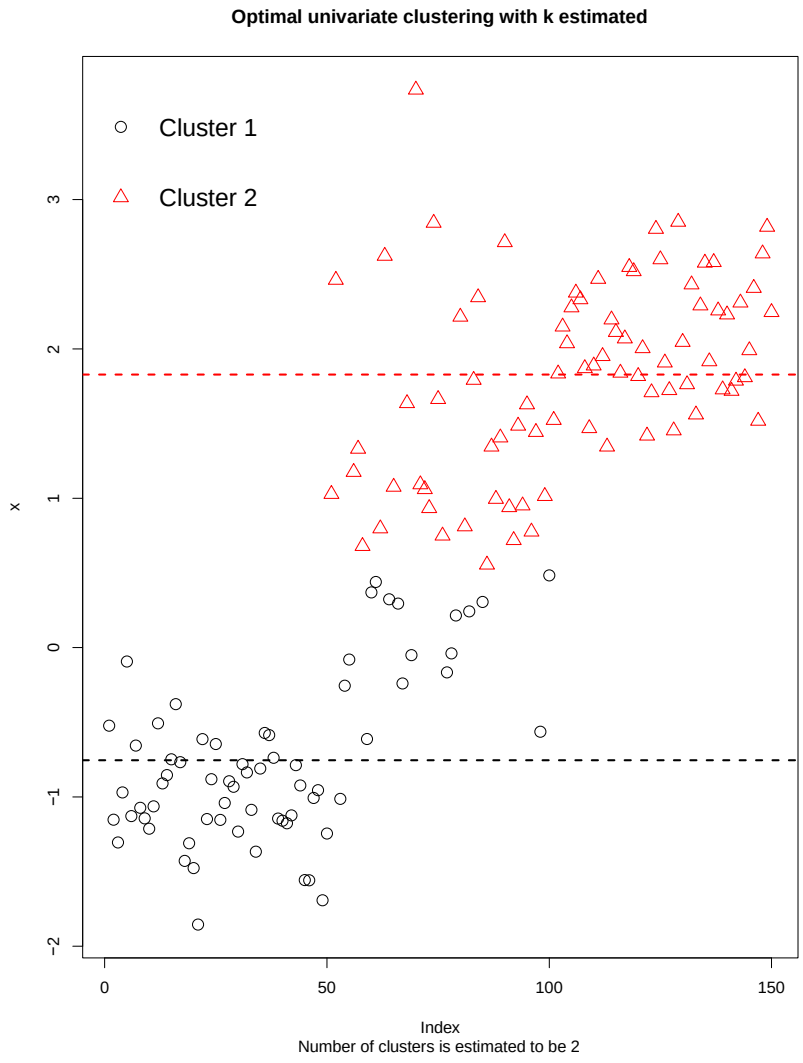

Figure 7: Two clusters were obtained from applying the ckmeans.1d.dp function on x= SPQ_positive scores sampled from a Gaussian mixture model estimated with two components. The horizontal axis represents the index number of each point in the data. The dotted lines represent the centres of each cluster.

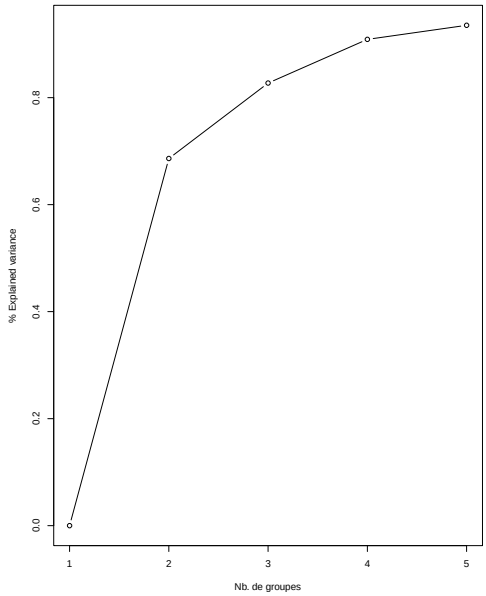

Figure 8: Elbow method for 2-solution cluster validation.

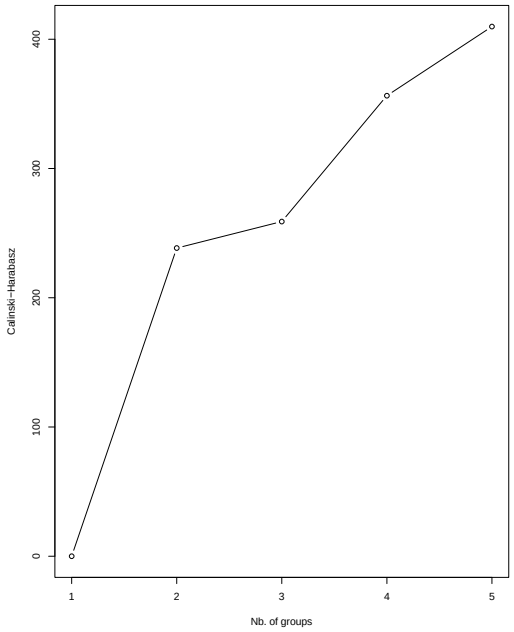

Figure 9: Calinski-Haarabasz method for 2-solution cluster validation.

SPQ Negative dimension

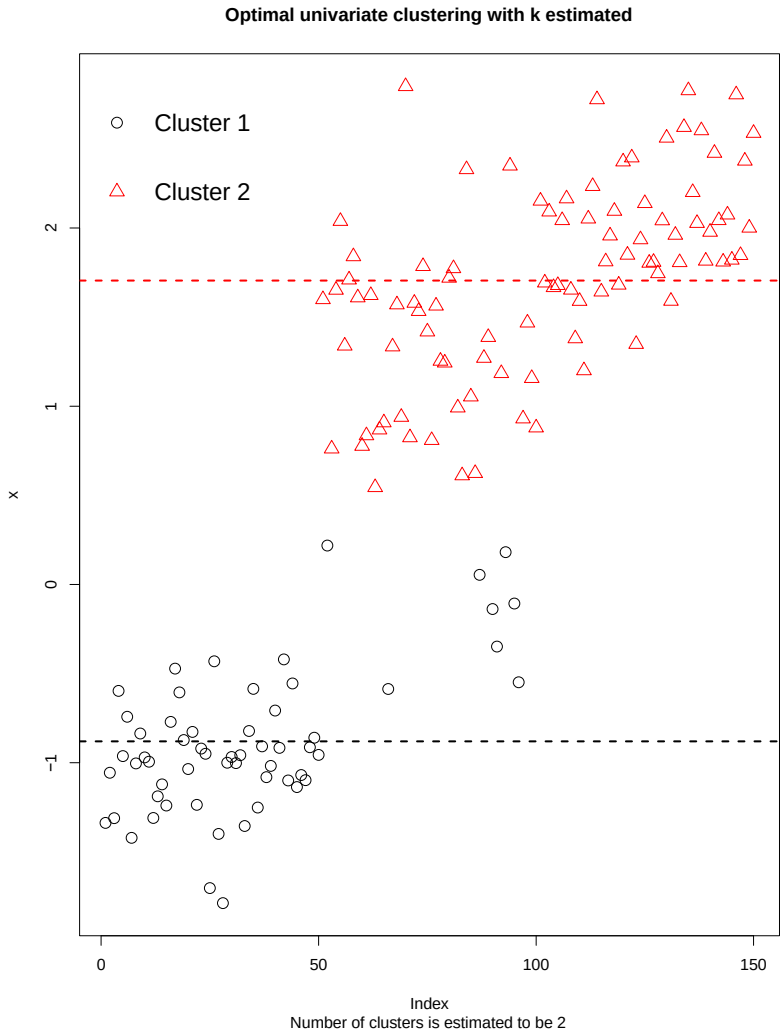

Figure 10: Two clusters were obtained from applying the ckmeans.1d.dp function on x= SPQ_negative scores sampled from a Gaussian mixture model estimated with two components. The horizontal axis represents the index number of each point in the data. The dotted lines represent the centres of each cluster.

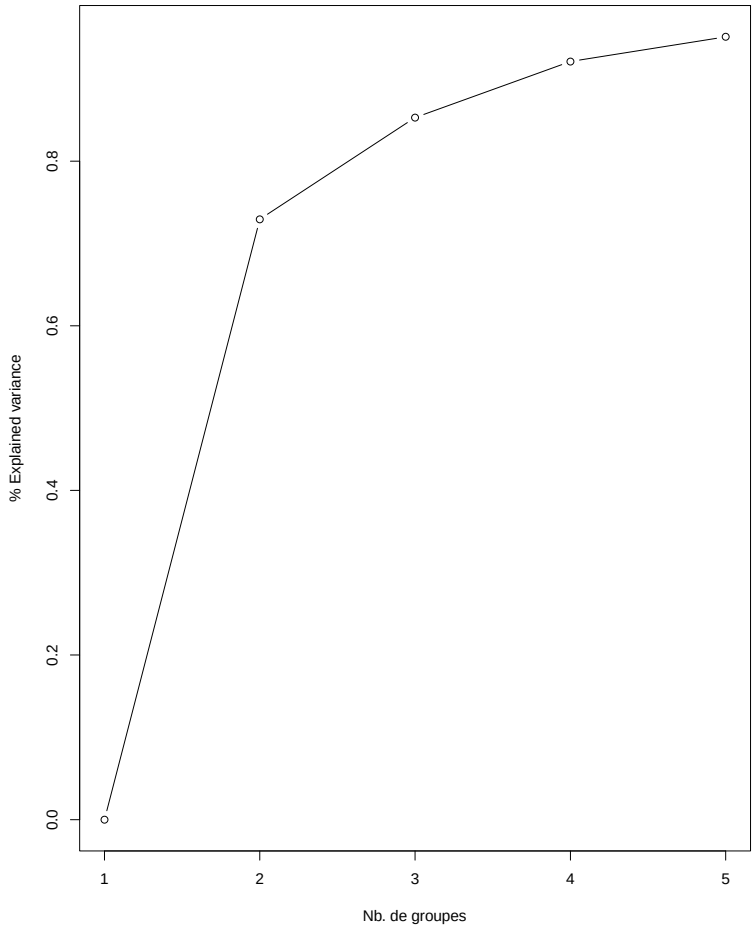

Figure 11: Elbow method for 2-solution cluster validation.

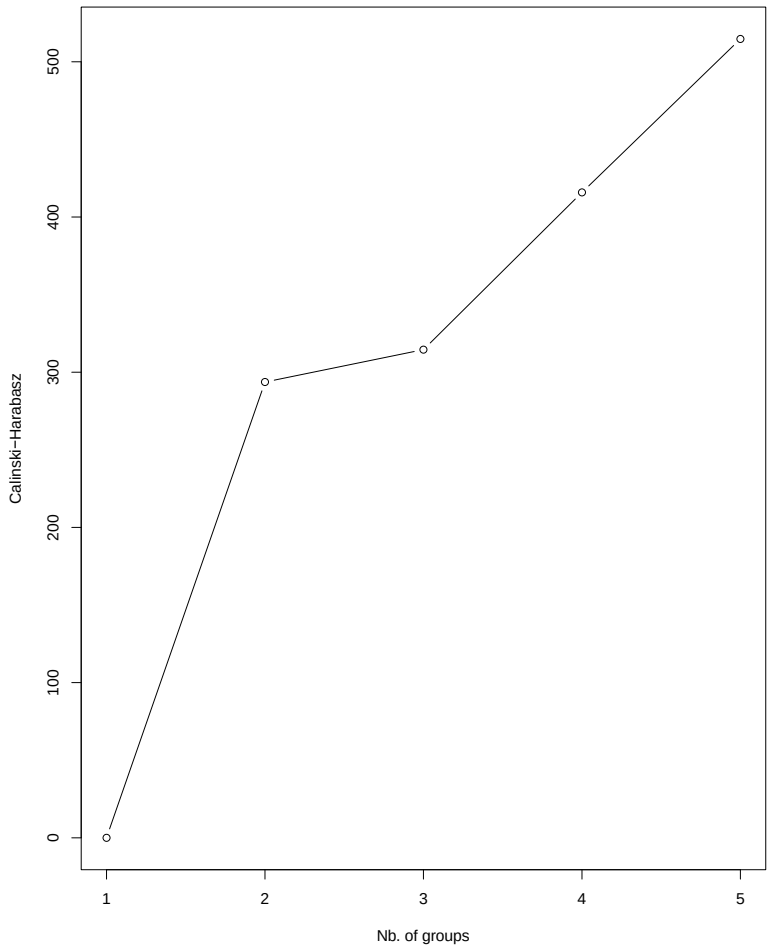

Figure 12: Calinski-Haarabasz method for 2-solution cluster validation.

4.2. Mutlivariate Analyses – 3 dimensions:

We performed multivariate analyses for the three dimensions combined (positive, negative, disorganized). Rows represented participants (n=109) and the three columns represented the raw scores per participants on the three dimensions. There were no missing values and data was standardized.

To determine the optimal number of clusters we computed different internal validation indices indicating the efficient number of clusters, including connectivity, silhouette and Dunn indices. Results provided for a clustering into 3 different groups. To do so we used functions from the clValid R package[12].

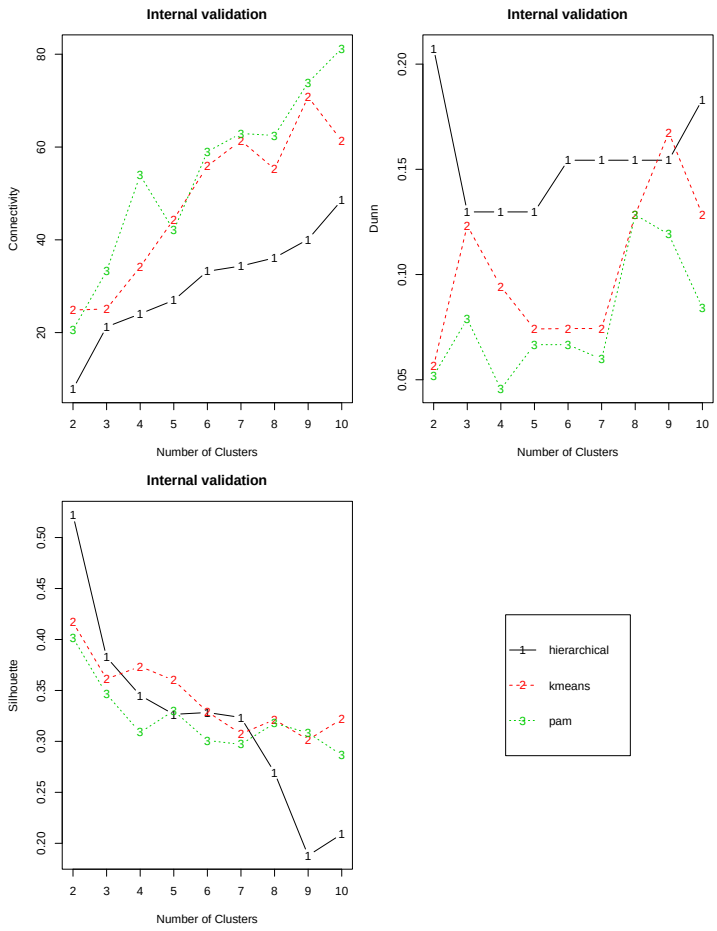

Figure 13: Internal validation indices provided for a 3-cluster solution.

The **connectivity measure** corresponds to what extent items are placed in the same cluster as their nearest neighbors in the data space. The value ranges between 0 and infinity and should be minimized to attest for efficient clustering. In this case the Connectivity measure seems to

be in favour of a 2-clusters solution for the hierarchical method, although for k-mean clustering methods the value is equal for a 2 or 3-cluster solution.

The **Dunn index** is computed as the distance between each of the objects in the cluster and objects in the other clusters. The Dunn index should be maximised to represent a good cluster solution. For hierarchical and k-means methods, the Dunn index is maximised for the 3-cluster solution, which seems to be the most consistent compared to the 2-cluster solution.

The **average silhouette** (last graph) method determines how well each object lies within its cluster. A high average silhouette width indicates a good clustering. Again, we could hesitate between a 2 and 3-cluster solutions, but consistency between k-means and hierarchical methods is seen for the solution with 3-clusters.

Considering the aforementioned observations, a 3 clusters solution appeared to be the optimal solution when compared with the others.

Hierarchical clustering starts by treating each observation as a separate cluster, then it repeatedly executes two steps: identify the two clusters that are closer together and merge the two most similar clusters. Repetition of these two steps continue until all the cluster are merged together.

Kmeans clustering algorithm identifies k number of centroids, and then allocates every data point to the nearest cluster, while keeping the centroids as small as possible.

PAM clustering (partition around medoids) is intended to find a sequence of medoids that are centrally located in clusters. The algorithm minimizes the average dissimilarity of objects to their closest selected object.

To further test for the stability of the chosen 3 clusters, we computed stability measures. This algorithm compares results from clustering based on the full data to clustering based on removing each column on at a time. The included measures were:

- Average proportion of non-overlap (APN) = 0.1419422
- Average Distance (AD) = 1.7357395
- Average Distance Between Means (ADM) = 0.5967227
- Figure of Merit (FOM) = 0.8561013

The values for APN, ADM and FOM ranges from 0 to 1 with smaller values corresponding to highly consistent clustering results. AD has a value ranging from 0 to infinity and smaller values are also preferred.

APN measures average proportion of observations not placed in the same cluster by clustering based on the full data and clustering based in the data with a single column removed.

AD measures the average distance between observations placed in the same cluster under both situation (full data and removal of 1 column).

ADM measures the average distance between clusters centres of observations placed in the same cluster under both situations.

FOM measures the average intra-cluster variance of the deleted column (clustering is based on the remaining columns).

After determining the stability of the three cluster solutions, we computed the cluster analysis to get the partitioning of participants into groups following scripts provided by the following website and we tried two different procedures: https://www.statmethods.net/advstats/cluster.html. We used the two distinct procedures to check whether participants were partitioned in the same groups or clusters, which was the case.

We first partitioned the data using K-means clustering (kmeans function in R with 3 solutions).

Secondly, we used Ward hierarchical agglomerative clustering and showed a dendrogram with 3 solutions.

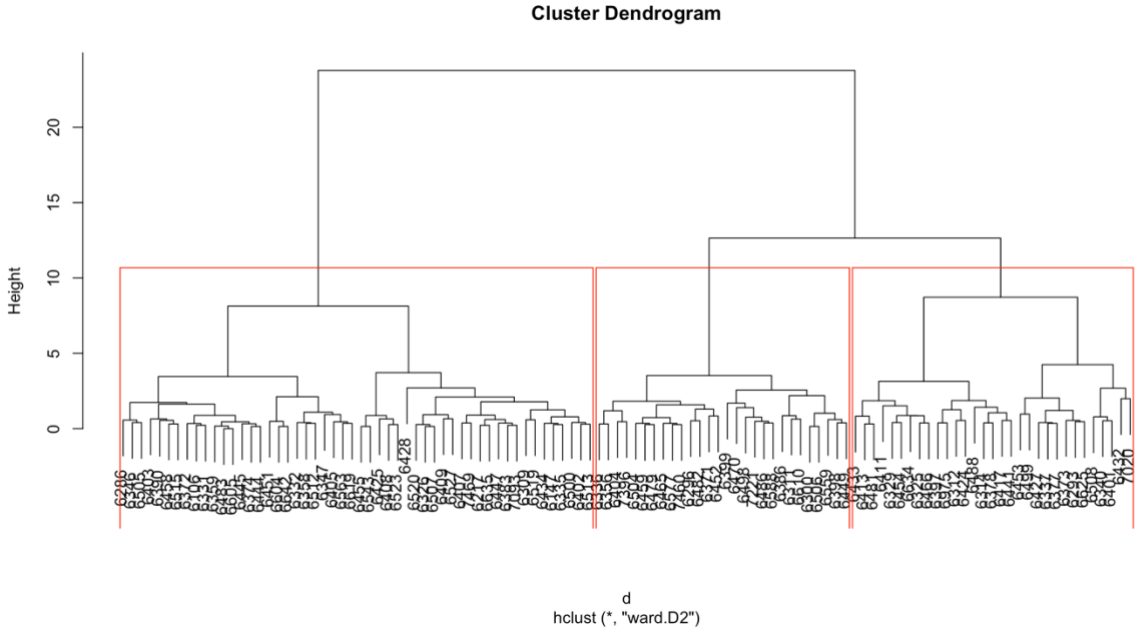

Figure 14: Dendrogram computed for three solution clusters using Ward hierarchical agglomerative method.

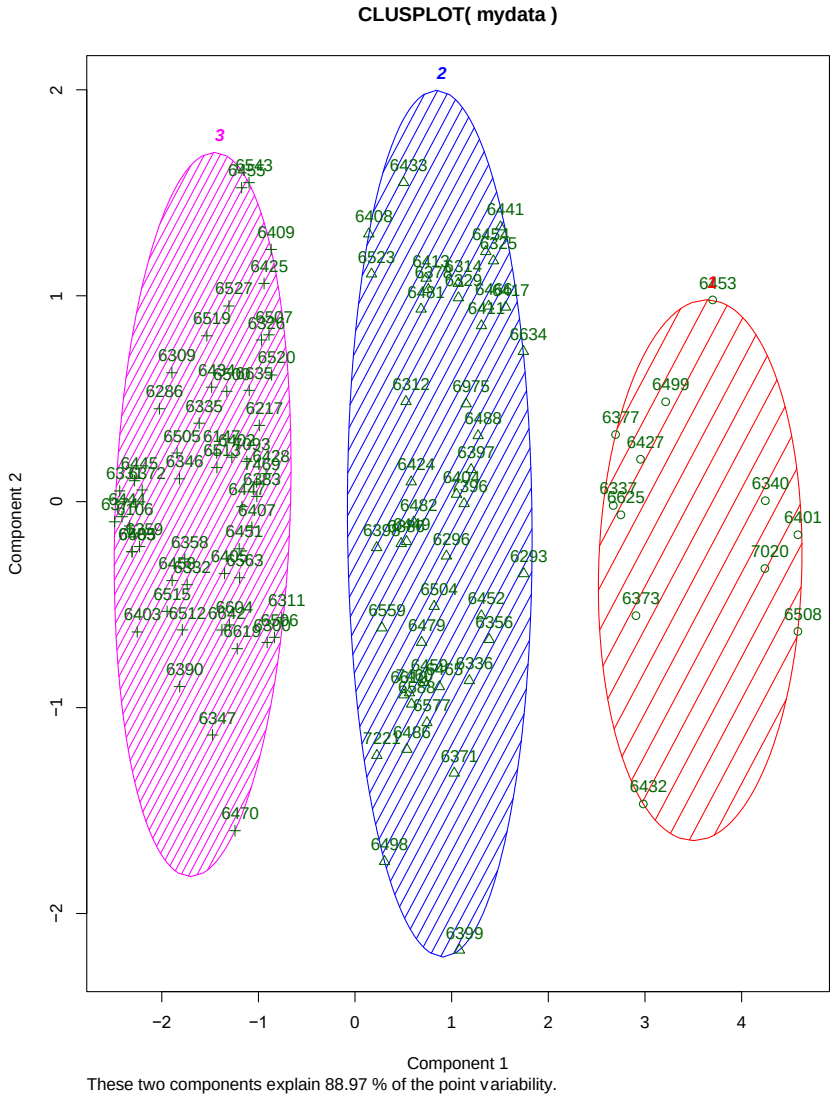

Figure 15: The clusplot function in R creates a bivariate plot visualizing a partition of the data using principal component scaling. All observations are represented by the participants' IDs and ellipses are drawn around each cluster.

The clusplot algorithm used PCA to draw the data. It uses the first two principal components to explain the data. Principal component are the orthogonal axes that along them the data has the most variability[13].

7. Mixed regression models statistical analyses

For each analysis, the algorithm tested four models, constant, linear, quadratic and cubic and retained the best fit using Bayesian Information Criterion (BIC), which translates in better describing the cortical thickness developmental trajectory in each of schizotypy groups.

Likelihood ratio test was used to compare the retained model in each group, yielding two types of significant differences:

- Intercept difference: described as a main effect of group. Data of both groups can be best explained by the same model type, while difference of CT values between groups is constant along time.

- Slope difference: represented Group x Time interaction effect, in which model types differed between group or both groups are explained by the same model type while difference of CT values between groups is not constant over time.

Bayesian Information Criterion (BIC):

When using BIC to retain the best model order, we obtain e.g., a full quadratic model with the following equation:

$$Y_{ij} = \beta_0 + \beta_{g1} \cdot g_i + \beta_{a1} \cdot a_{ij} + \beta_{ag1} \cdot g_i \cdot a_{ij} + \beta_{a2} \cdot a^2_{ij} + \beta_{ag2} \cdot g_i \cdot a^2_{ij} + u_{i0} + u_{i1} \cdot a_{ij} + \epsilon_{ij}$$

Y: cortical thickness

i,j:[subjects,scan]index

β_{xn}*: fixed effects*

g: grouping variable

a: age

u: normally distributed random effect

ϵ_{ij} *: normally distributed error term*

When using log-likelihood ratio to test for between-groups differences in intercept and slope, we tested the full model against the following reduced models.

- Reduced group effect model:

$$Y_{ij} = \beta_0 + \beta_{a1} \,.\, a_{ij} + \beta_{a2} \,.\, a^2_{ij} + u_{i0} + u_{i1} \,.\, a_{ij} + \epsilon_{ij}$$

- Reduced slope model:

$$Y_{ij} = \beta_0 + \beta_{g1} \,.\, g_i + \beta_{a1} \,.\, a_{ij} + \beta_{a2} \,.\, a^2_{ij} + u_{i0} + u_{i1} \,.\, a_{ij} + \epsilon_{ij}$$

8. Analyses conducted

For each analysis we included the same covariates when performing mixed models analyses.

Then we did 8 different analyses:

- Right hemisphere: Comparison between high positive and low positive schizotypy
- Left hemisphere: Comparison between high positive and low positive schizotypy
- Right hemisphere: Comparison between high negative and low negative schizotypy
- Left hemisphere: Comparison between high negative and low negative schizotypy
- Right hemisphere: Comparison between high disorganized and low disorganized schizotypy
- Left hemisphere: Comparison between high disorganized and low disorganized schizotypy
- Right hemisphere: Comparison between high in all dimension VS intermediate in all dimensions VS low in all dimensions
- Left hemisphere: Comparison between high in all dimension VS intermediate in all dimensions VS low in all dimensions

9. Significant results

Schizotypy		CT regions	Model fitted	Shape *p* value	Intercept *p* value
A. Dimensions	Positive	L-posterior cingulate	Linear	*0.012*	*0.016*
	Negative	L-pars triangularis	Quadratic	*0.049*	*0.045*
	Negative	R-isthmus cingulate	Quadratic	*0.010*	*0.010*
	Negative	L-lateral orbitofrontal	Quadratic	*0.001*	*0.0004*

	Negative	L-rostral middle frontal	Quadratic	*0.013*	*0.004*
	Negative	R-lateral occipital	Quadratic	*0.0004*	*0.0002*
	Disorganized	R-caudal anterior cingulate	Linear	*0.034*	*0.009*
B. Profiles		R-isthmus cingulate	Quadratic	*0.010*	*0.005*
		R-lateral occipital	Quadratic	*0.013*	*0.005*

Differences in longitudinal trajectories between groups. Significant values after correction for multiple comparisons with FDR procedure (p <0.05) are displayed in italics.

10. All Results – Group and interaction effects tables

3 dimensions Left hemisphere

modelName	modelOrder	pValGroup	pValInteraction
lh_caudalanteriorcingulate_thickness	2	0.56291753	0.48582551
lh_caudalmiddlefrontal_thickness	1	0.88450824	0.64236472
lh_cuneus_thickness	0	0.98849998	0
lh_entorhinal_thickness	0	0.24809596	0
lh_fusiform_thickness	1	0.29888699	0.1467665
lh_inferiorparietal_thickness	2	0.42579586	0.26827412
lh_inferiortemporal_thickness	1	0.64413253	0.46350929
lh_isthmuscingulate_thickness	1	0.2460124	0.22249667
lh_lateraloccipital_thickness	1	0.48367463	0.39698318
lh_lateralorbitofrontal_thickness	1	0.55285014	0.47403794
lh_lingual_thickness	0	0.19497753	0
lh_medialorbitofrontal_thickness	0	0.99770734	0
lh_middletemporal_thickness	1	0.98862655	0.88729375
lh_parahippocampal_thickness	0	0.49195687	0
lh_paracentral_thickness	0	0.80675771	0
lh_parsopercularis_thickness	1	0.63637062	0.86595546
lh_parsorbitalis_thickness	0	0.60599504	0

lh_parstriangularis_thickness	0	0.9505387	0
lh_pericalcarine_thickness	0	0.97164303	0
lh_postcentral_thickness	1	0.94463079	0.99489555
lh_posteriorcingulate_thickness	1	0.05332956	0.08571862
lh_precentral_thickness	0	0.15933134	0
lh_precuneus_thickness	1	0.76179648	0.49231204
lh_rostralanteriorcingulate_thickness	0	0.15600704	0
lh_rostralmiddlefrontal_thickness	1	0.54098494	0.96990187
lh_superiorfrontal_thickness	1	0.64362272	0.35436229
lh_superiorparietal_thickness	0	0.55756707	0
lh_superiortemporal_thickness	0	0.55478861	0
lh_supramarginal_thickness	2	0.09096914	0.05133525
lh_frontalpole_thickness	1	0.26304982	0.21885951
lh_temporalpole_thickness	0	0.35177567	0
lh_transversetemporal_thickness	0	0.92428573	0
lh_insula_thickness	1	0.75263184	0.57041089

3 dimensions Right hemisphere

modelName	modelOrder	pValGroup	pValInteraction

rh_caudalanteriorcingulate_thickness	1	0.93097798	0.82760244
rh_caudalmiddlefrontal_thickness	1	0.73458258	0.98988788
rh_cuneus_thickness	0	0.99314004	0
rh_entorhinal_thickness	0	0.47436552	0
rh_fusiform_thickness	1	0.2805506	0.13680028
rh_inferiorparietal_thickness	2	0.40258928	0.23111556
rh_inferiortemporal_thickness	1	0.63851698	0.3525672
rh_isthmuscingulate_thickness	2	0.01069886	0.00521063
rh_lateraloccipital_thickness	2	0.01356063	0.00485318
rh_lateralorbitofrontal_thickness	1	0.96973807	0.88038901
rh_lingual_thickness	0	0.49014602	0
rh_medialorbitofrontal_thickness	1	0.46360644	0.48516737
rh_middletemporal_thickness	1	0.62470171	0.60417523
rh_parahippocampal_thickness	0	0.99866381	0
rh_paracentral_thickness	0	0.94021403	0
rh_parsopercularis_thickness	0	0.9878641	0
rh_parsorbitalis_thickness	0	0.85141799	0
rh_parstriangularis_thickness	0	0.95375179	0
rh_pericalcarine_thickness	0	0.51491072	0

rh_postcentral_thickness	1	0.24650539	0.83351689
rh_posteriorcingulate_thickness	1	0.52829765	0.2629385
rh_precentral_thickness	0	0.3752911	0
rh_precuneus_thickness	2	0.55467297	0.35256726
rh_rostralanteriorcingulate_thickness	1	0.20545113	0.59779809
rh_rostralmiddlefrontal_thickness	1	0.77771691	0.48770852
rh_superiorfrontal_thickness	1	0.73503015	0.45596138
rh_superiorparietal_thickness	1	0.99976664	0.99714465
rh_superiortemporal_thickness	0	0.83449351	0
rh_supramarginal_thickness	2	0.06972913	0.0577756
rh_frontalpole_thickness	1	0.08935092	0.85462015
rh_temporalpole_thickness	0	0.73559677	0
rh_transversetemporal_thickness	0	0.9733069	0
rh_insula_thickness	0	0.98553323	0

Disorganized dimension Left hemisphere

modelName	modelOrder	pValGroup	pValInteraction
lh_caudalanteriorcingulate_thickness	2	0.16800224	0.08707129
lh_caudalmiddlefrontal_thickness	1	0.31385421	0.13985453

lh_cuneus_thickness	0	0.70637317	0
lh_entorhinal_thickness	0	0.99738685	0
lh_fusiform_thickness	1	0.54964233	0.77020979
lh_inferiorparietal_thickness	2	0.32144859	0.42941672
lh_inferiortemporal_thickness	1	0.10833169	0.6264964
lh_isthmuscingulate_thickness	1	0.84835867	0.58287469
lh_lateraloccipital_thickness	1	0.86306031	0.59821795
lh_lateralorbitofrontal_thickness	1	0.10925229	0.05138575
lh_lingual_thickness	0	0.0895132	0
lh_medialorbitofrontal_thickness	0	0.63593356	0
lh_middletemporal_thickness	1	0.23797782	0.71791723
lh_parahippocampal_thickness	0	0.93069507	0
lh_paracentral_thickness	0	0.55215218	0
lh_parsopercularis_thickness	1	0.07241077	0.21406157
lh_parsorbitalis_thickness	0	0.39617286	0
lh_parstriangularis_thickness	1	0.43190843	0.20521879
lh_pericalcarine_thickness	0	0.50210243	0
lh_postcentral_thickness	1	0.35377934	0.86044749
lh_posteriorcingulate_thickness	1	0.71402865	0.77487305

lh_precentral_thickness	0	0.07506282	0
lh_precuneus_thickness	1	0.88042647	0.90936004
lh_rostralanteriorcingulate_thickness	0	0.72736212	0
lh_rostralmiddlefrontal_thickness	1	0.26882688	0.13640478
lh_superiorfrontal_thickness	1	0.13855218	0.0592487
lh_superiorparietal_thickness	0	0.27915207	0
lh_superiortemporal_thickness	0	0.47095291	0
lh_supramarginal_thickness	2	0.18143817	0.39352606
lh_frontalpole_thickness	1	0.79112251	0.73824351
lh_temporalpole_thickness	0	0.06340335	0
lh_transversetemporal_thickness	0	0.9593181	0
lh_insula_thickness	1	0.27177944	0.96952954

Disorganized dimension Right hemisphere

modelName	modelOrder	pValGroup	pValInteraction
rh_caudalanteriorcingulate_thickness	1	0.03382153	0.00925834
rh_caudalmiddlefrontal_thickness	1	0.70581689	0.54650797
rh_cuneus_thickness	0	0.80580543	0
rh_entorhinal_thickness	0	0.21010187	0

rh_fusiform_thickness	1	0.29921353	0.56537478
rh_inferiorparietal_thickness	2	0.50307972	0.61654876
rh_inferiortemporal_thickness	1	0.55924568	0.9379977
rh_isthmuscingulate_thickness	2	0.29755644	0.81832233
rh_lateraloccipital_thickness	1	0.94891787	0.92613786
rh_lateralorbitofrontal_thickness	1	0.40039359	0.19974708
rh_lingual_thickness	0	0.29441918	0
rh_medialorbitofrontal_thickness	1	0.59884452	0.31482126
rh_middletemporal_thickness	1	0.0765435	0.27915982
rh_parahippocampal_thickness	0	0.0498446	0
rh_paracentral_thickness	0	0.75919347	0
rh_parsopercularis_thickness	0	0.57470787	0
rh_parsorbitalis_thickness	0	0.36811466	0
rh_parstriangularis_thickness	0	0.75516585	0
rh_pericalcarine_thickness	0	0.9361627	0
rh_postcentral_thickness	1	0.40000365	0.6373571
rh_posteriorcingulate_thickness	1	0.80263411	0.56574775
rh_precentral_thickness	0	0.31995108	0
rh_precuneus_thickness	2	0.70710168	0.55706633

rh_rostralanteriorcingulate_thickness	1	0.44401795	0.21050091
rh_rostralmiddlefrontal_thickness	1	0.48513737	0.23857669
rh_superiorfrontal_thickness	1	0.11167237	0.07668255
rh_superiorparietal_thickness	1	0.90596251	0.90081302
rh_superiortemporal_thickness	0	0.99989621	0
rh_supramarginal_thickness	2	0.08374824	0.07208732
rh_frontalpole_thickness	1	0.37340903	0.45826071
rh_temporalpole_thickness	0	0.0727538	0
rh_transversetemporal_thickness	0	0.69234831	0
rh_insula_thickness	0	0.56647712	0

Negative dimension Left hemisphere

modelName	modelOrder	pValGroup	pValInteraction
lh_caudalanteriorcingulate_thickness	2	0.29203826	0.52563391
lh_caudalmiddlefrontal_thickness	1	0.06090681	0.11526858
lh_cuneus_thickness	0	0.99391832	0
lh_entorhinal_thickness	0	0.38330159	0
lh_fusiform_thickness	1	0.36972627	0.37027055
lh_inferiorparietal_thickness	2	0.11396523	0.08591623

lh_inferiortemporal_thickness	1	0.77578245	0.53447691
lh_isthmuscingulate_thickness	1	0.41415662	0.48438433
lh_lateraloccipital_thickness	1	0.71341543	0.66039919
lh_lateralorbitofrontal_thickness	2	0.00125052	0.00038548
lh_lingual_thickness	0	0.45786928	0
lh_medialorbitofrontal_thickness	0	0.3295672	0
lh_middletemporal_thickness	1	0.6691643	0.6312212
lh_parahippocampal_thickness	0	0.96133169	0
lh_paracentral_thickness	0	0.49550079	0
lh_parsopercularis_thickness	1	0.12951906	0.46210096
lh_parsorbitalis_thickness	0	0.7761056	0
lh_parstriangularis_thickness	2	0.04872459	0.04501627
lh_pericalcarine_thickness	0	0.72732572	0
lh_postcentral_thickness	1	0.69630722	0.5839316
lh_posteriorcingulate_thickness	1	0.29304618	0.40853153
lh_precentral_thickness	0	0.03581266	0
lh_precuneus_thickness	1	0.84588515	0.91069127
lh_rostralanteriorcingulate_thickness	0	0.87052136	0
lh_rostralmiddlefrontal_thickness	2	0.01278599	0.004556

lh_superiorfrontal_thickness	1	0.31419591	0.74445219
lh_superiorparietal_thickness	0	0.31265959	0
lh_superiortemporal_thickness	0	0.15470708	0
lh_supramarginal_thickness	0	0.27989993	0
lh_frontalpole_thickness	1	0.58249691	0.43772534
lh_temporalpole_thickness	0	0.1870895	0
lh_transversetemporal_thickness	0	0.52140458	0
lh_insula_thickness	1	0.8532168	0.93594194

Negative dimension Right hemisphere

modelName	modelOrder	pValGroup	pValInteraction
rh_caudalanteriorcingulate_thickness	1	0.8972523	0.67193817
rh_caudalmiddlefrontal_thickness	1	0.11212139	0.38743569
rh_cuneus_thickness	0	0.89721644	0
rh_entorhinal_thickness	0	0.3164049	0
rh_fusiform_thickness	1	0.15410919	0.14191565
rh_inferiorparietal_thickness	2	0.33448793	0.28249341
rh_inferiortemporal_thickness	1	0.45212702	0.20891939
rh_isthmuscingulate_thickness	2	0.00970179	0.01018215

rh_lateraloccipital_thickness	2	0.00036273	0.00018715
rh_lateralorbitofrontal_thickness	1	0.6917895	0.61425951
rh_lingual_thickness	0	0.99184344	0
rh_medialorbitofrontal_thickness	1	0.08740528	0.04862986
rh_middletemporal_thickness	1	0.24473911	0.48646516
rh_parahippocampal_thickness	0	0.62195161	0
rh_paracentral_thickness	0	0.25436246	0
rh_parsopercularis_thickness	0	0.40672205	0
rh_parsorbitalis_thickness	0	0.79460035	0
rh_parstriangularis_thickness	0	0.13075369	0
rh_pericalcarine_thickness	0	0.3565179	0
rh_postcentral_thickness	1	0.42479112	0.42228125
rh_posteriorcingulate_thickness	1	0.66048842	0.36285789
rh_precentral_thickness	0	0.11657696	0
rh_precuneus_thickness	2	0.74899527	0.5443127
rh_rostralanteriorcingulate_thickness	1	0.1002356	0.16022154
rh_rostralmiddlefrontal_thickness	1	0.87538899	0.62729293
rh_superiorfrontal_thickness	1	0.27212254	0.86874986
rh_superiorparietal_thickness	1	0.89992034	0.68808449

rh_superiortemporal_thickness	0	0.1733284	0
rh_supramarginal_thickness	2	0.0696935	0.06619754
rh_frontalpole_thickness	1	0.0910733	0.56118456
rh_temporalpole_thickness	0	0.10432342	0
rh_transversetemporal_thickness	0	0.72617056	0
rh_insula_thickness	0	0.85942243	0

Positive dimension Left hemisphere

modelName	modelOrder	pValGroup	pValInteraction
lh_caudalanteriorcingulate_thickness	2	0.30836456	0.35563427
lh_caudalmiddlefrontal_thickness	1	0.66520849	0.71074863
lh_cuneus_thickness	0	0.82693763	0
lh_entorhinal_thickness	0	0.85232044	0
lh_fusiform_thickness	1	0.46096164	0.32758817
lh_inferiorparietal_thickness	2	0.40251672	0.28724843
lh_inferiortemporal_thickness	1	0.8824657	0.62674885
lh_isthmuscingulate_thickness	1	0.22355115	0.22024154
lh_lateraloccipital_thickness	1	0.405848	0.29824139

lh_lateralorbitofrontal_thickness	1	0.83187174	0.5440378
lh_lingual_thickness	0	0.99960073	0
lh_medialorbitofrontal_thickness	0	0.3513747	0
lh_middletemporal_thickness	1	0.78356034	0.92303688
lh_parahippocampal_thickness	0	0.40808234	0
lh_paracentral_thickness	0	0.34749387	0
lh_parsopercularis_thickness	1	0.71023708	0.54555951
lh_parsorbitalis_thickness	0	0.37781903	0
lh_parstriangularis_thickness	1	0.19010268	0.18614395
lh_pericalcarine_thickness	0	0.78339007	0
lh_postcentral_thickness	1	0.74066949	0.76660367
lh_posteriorcingulate_thickness	1	0.0122766	0.01572851
lh_precentral_thickness	0	0.71772448	0
lh_precuneus_thickness	1	0.50025106	0.25103442
lh_rostralanteriorcingulate_thickness	0	0.05247899	0
lh_rostralmiddlefrontal_thickness	1	0.17633386	0.51663875
lh_superiorfrontal_thickness	1	0.35132498	0.22144592
lh_superiorparietal_thickness	0	0.62042013	0
lh_superiortemporal_thickness	0	0.77856087	0

lh_supramarginal_thickness	2	0.12818168	0.07084774
lh_frontalpole_thickness	1	0.2259413	0.10267936
lh_temporalpole_thickness	0	0.72234809	0
lh_transversetemporal_thickness	0	0.35538904	0
lh_insula_thickness	1	0.95999992	0.92242899

Positive dimension Right hemisphere

modelName	modelOrder	pValGroup	pValInteraction
rh_caudalanteriorcingulate_thickness	1	0.2053759	0.90002535
rh_caudalmiddlefrontal_thickness	1	0.8616518	0.86334829
rh_cuneus_thickness	0	0.68012051	0
rh_entorhinal_thickness	0	0.50920731	0
rh_fusiform_thickness	1	0.23502712	0.17955297
rh_inferiorparietal_thickness	2	0.30370851	0.20021231
rh_inferiortemporal_thickness	1	0.62601911	0.3545418
rh_isthmuscingulate_thickness	2	0.08049797	0.06457003
rh_lateraloccipital_thickness	1	0.5975409	0.33656069
rh_lateralorbitofrontal_thickness	1	0.95614848	0.87274637
rh_lingual_thickness	0	0.91274142	0

rh_medialorbitofrontal_thickness	1	0.58771435	0.51714772
rh_middletemporal_thickness	1	0.80011942	0.50444031
rh_parahippocampal_thickness	0	0.94608374	0
rh_paracentral_thickness	0	0.30448692	0
rh_parsopercularis_thickness	0	0.35666715	0
rh_parsorbitalis_thickness	0	0.9407143	0
rh_parstriangularis_thickness	0	0.28199582	0
rh_pericalcarine_thickness	0	0.88923609	0
rh_postcentral_thickness	1	0.21045154	0.70252983
rh_posteriorcingulate_thickness	1	0.405627	0.21154551
rh_precentral_thickness	0	0.96812723	0
rh_precuneus_thickness	2	0.26027033	0.1441302
rh_rostralanteriorcingulate_thickness	1	0.23639733	0.54004051
rh_rostralmiddlefrontal_thickness	1	0.14278886	0.28358788
rh_superiorfrontal_thickness	1	0.15205574	0.36043933
rh_superiorparietal_thickness	1	0.29430309	0.274582
rh_superiortemporal_thickness	0	0.62204525	0
rh_supramarginal_thickness	2	0.38177889	0.21952233
rh_frontalpole_thickness	1	0.33419248	0.55418316

rh_temporalpole_thickness	0	0.82963653	0
rh_transversetemporal_thickness	0	0.7841864	0
rh_insula_thickness	0	0.91038717	0

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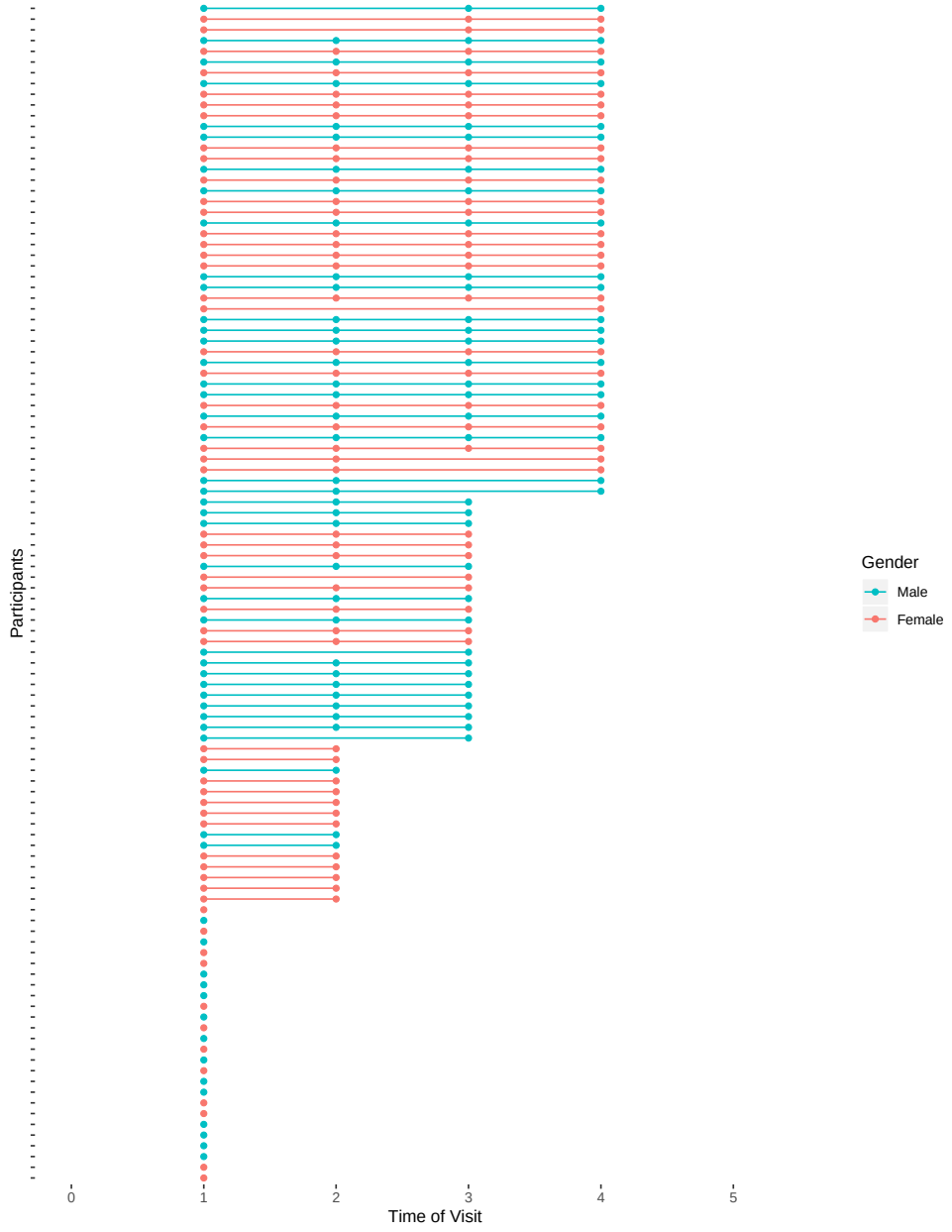
Appendix 4.

Supplementary material – Study 2

1. Number of visits



Supplementary Figure 1**:** Distribution of participants' time of visit: 110 participants were scanned at first visit, 77 of them were scanned at the second visit, 64 at the third, 46 at the fourth and 12 at the fifth.

	T1	**T2**	**T3**	**T4**

Mean(age)	16.00	17.34	18.47	21.06
SD(age)	1.83	1.84	2.09	1.94
N	110	77	64	46
	T1-T2	**T2-T3**	**T3-T4**	
Mean Intervals between scans (days)	522.38	558.92	930.72	
SD (intervalls)	357.72	370.86	161.86	
N	78	60	40	

Supplementary Table 1: In this table, the upper part represents the number of participants scanned per visits, with the mean age and SD for each visit. The lower part represents the mean intervals (in days) between each scanning session.

For the 78 adolescents who were scanned at T1 and T2 consecutively, there was a mean interval of 522.38 days, for those who were scanned between T2 and T3 consecutively 558.92 days, between T3 and T4 930.72 days.

2. Exclusion criteria

Exclusion criteria included: acute psychotic phase, and estimated IQ scoring below 1 std.dev of the developmental norm (based on the Cubes and Vocabulary subtest of the Weschler Scales of Intelligence for children (WISC-IV)[1] or for participants older than 18 y.o, the Wechsler Adult Intelligence Scale[2] (WAIS-IV)). Screening was made through medical questionnaire asking for any previous psychiatric diagnosis, treatment, epilepsy, neurological disorders. We also ask them whether they are following or have followed in the past any medication. In

addition, they are asked whether they consult or have consulted psychiatrists or psychologists, or speech therapists. Questions concerning substance and alcohol use are asked as well in the medical screening questionnaire. Questions about their consumption quantity, as well as whether the consumption led to incompatibility with responsibilities (i.e. school) or to problems with the law were asked.

On this basis we excluded from the present study: 7 participants who suffered from diagnosed anxiety disorders and depression, 5 out of 7 were following psychopharmacological medication, notably for depressive symptoms (Cytralex and Sertraline). 4 other participants were diagnosed for ADHD and all of them were on medication (Concerta or Ritaline). One presented schizoaffective disorder combined with a neurological disorder and was thus also excluded from the sample. None of our participants had experienced epilepsy. None of our participant followed psychoactive treatment, none were excluded because of alcohol or substance abuse.

3. Socio demographic characteristics of the study participants

Ethnic

	1 = Suisse	2 = French	3 = Southern Europe	4 = North Africa	5 = South Africa	6 = Asia	7 = Mixed	8 = Others	Missing
N	35	9	7	0	3	0	29	13	14
Parents' SES									
Proffesional category	1= Dirigeants, senior executive..	2 = Academic and scientific professions	3 = Intermediate professions	4 = Administrative employés	5 = Customer service and sales personnel	6 = Farmers, hunters …	7 = Machine and industrial robots operators, crane operators, drivers … engib	8 = Workers and unskilled workers	Missing data
N	18	20	26	17	14	5	9	0	1
Formation level	1 = University & higher education	2 =Superior Proffesional schools	3 = A level	4 = Vocational school	5 = Apprenticeship	6 = compulsory school	7 =Less than compulsory school	8 = other	Missing data
N	56	4	9	4	19	15	2	0	1

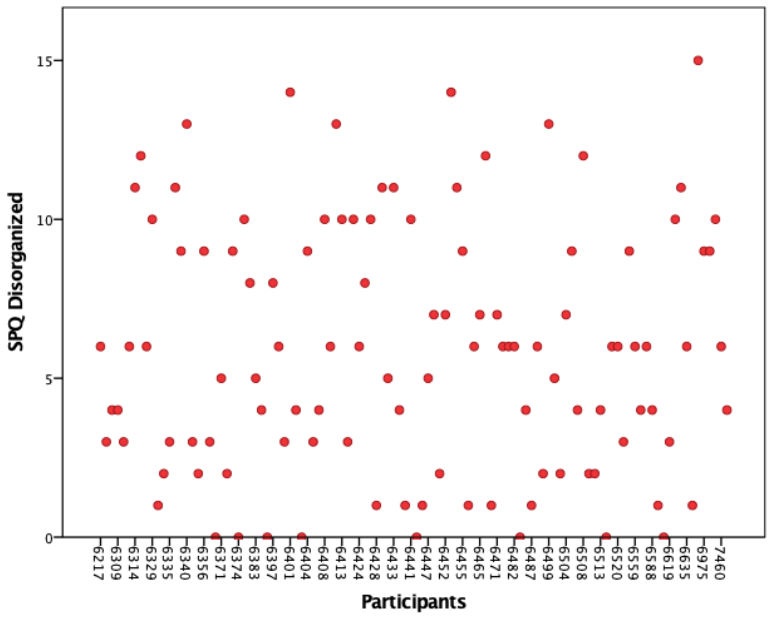
4. Psychological measures

Adaptive behaviors were assessed using the Youth self-reported questionnaire[3] (YSR) and, for participants of 18 y.o and older, with the Adult Self Report questionnaire[4] (ASR), yielding internalization (withdrawal, anxiety, depression, and somatic complaints) and externalization (attention problems, aggressive behaviors and delinquency) problem scores. These scores were used as covariates in the analyses to more effectively isolate the effect of schizotypy.

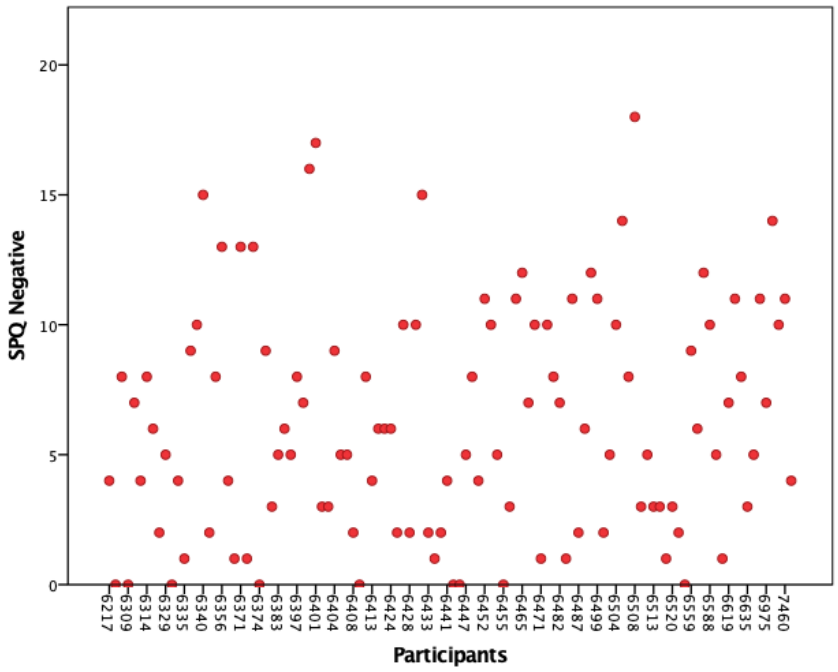
Schizotypal personality traits were assessed with a validated[5] French version of the SPQ[6]. It consists of a 74-item self-report questionnaire based on the nine DSM-IV criteria for schizotypal personality disorder. The positive dimension combines the subscales: ideas of reference, odd beliefs or magical thinking, unusual perceptual experiences, and suspiciousness. The negative dimension includes constricted affect, excessive social anxiety, and having no close friends. The disorganized schizotypy comprises odd or eccentric behavior, and odd speech.

5. Distribution of raw SPQ scores per dimensions

The Y-axis represents the raw scores on SPQ. The X-axis represents participants ID's.



Supplementary Figure 2: Distribution of the participants' raw scores on the disorganized dimension



Supplementary Figure 3: Distribution of the participants' raw scores on the negative dimension

6. Procedure followed for cluster analyses

All procedure followed for cluster analyses were conducted in R.

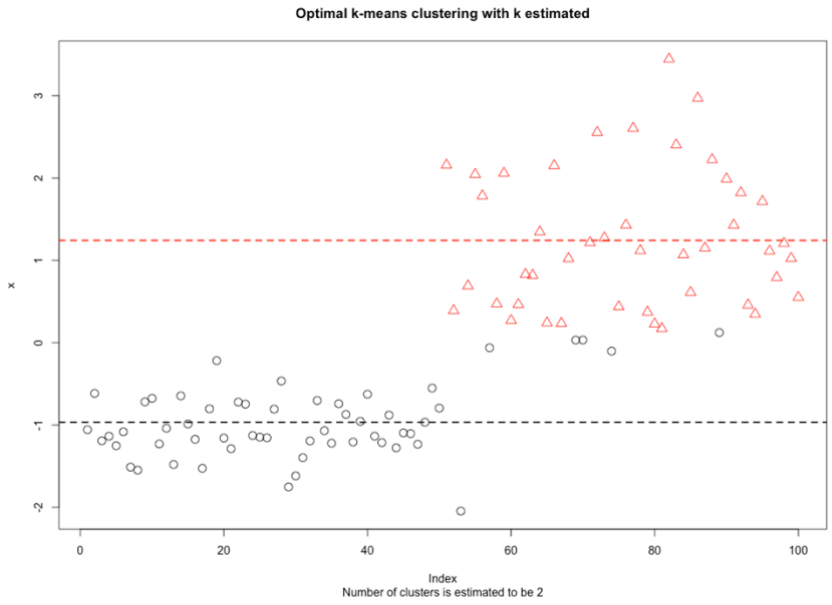
6.1 Univariate Analyses – Within dimensions:

For the univariate analyses we used optimal K-means clustering in One-dimension by dynamic programming (package: Ckmeans.1d.dp) implemented in R. This function performs optimal k-means clustering on one-dimensional data. In contrast to the heuristic k-means algorithms implemented for 3D data, this function assigns element in numeric vector into a number of clusters by dynamic programming[7]. It minimizes the sum of squares of within-cluster distances from each element to its corresponding cluster centre. When a range is provided for k, the exact number of clusters is determined by Bayesian information criterion. A resulting efficient number of 2 clusters per dimensions were returned.

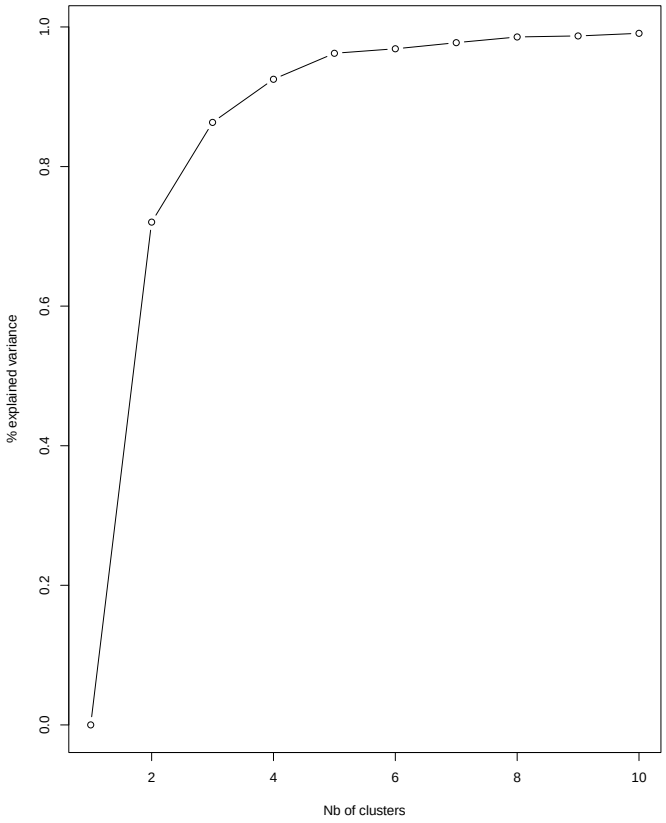
As a validation for cluster solution we computed elbow and calinski-harabasz methods and displayed their visualization.

Below are presented the estimation of correct number of clusters as determined by Bayesian criterion with the Ckmeans.1d.dp function and the validity measures obtained.

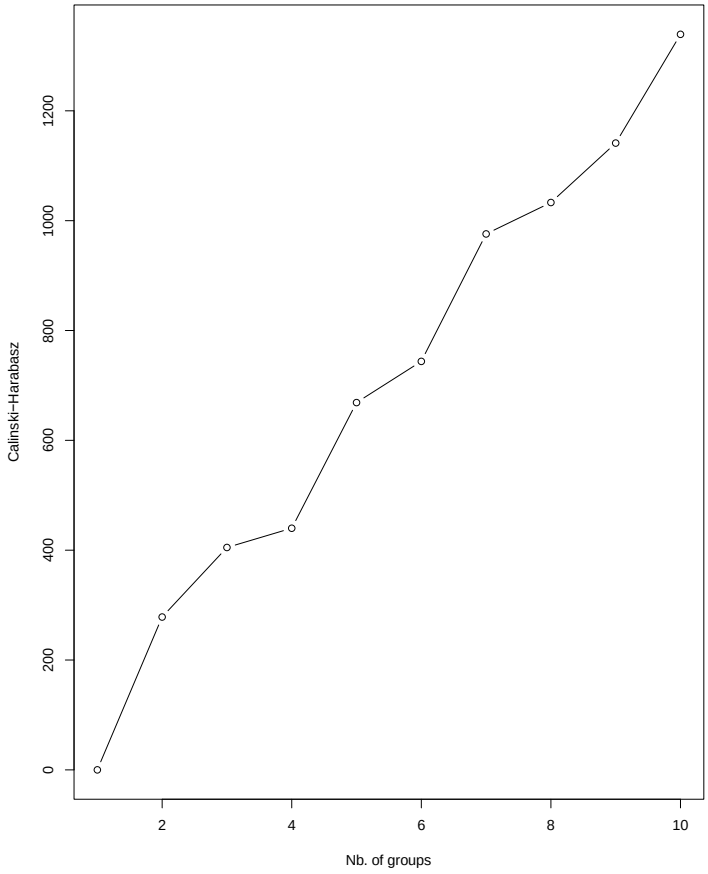
SPQ Disorganized dimension



Supplementary Figure 4: Two clusters were obtained from applying the ckmeans.1d.dp function on x= SPQ_disorganized scores sampled from a Gaussian mixture model estimated with two components. The horizontal axis represents the index number of each point in the data. The dotted lines represent the centres of each cluster.

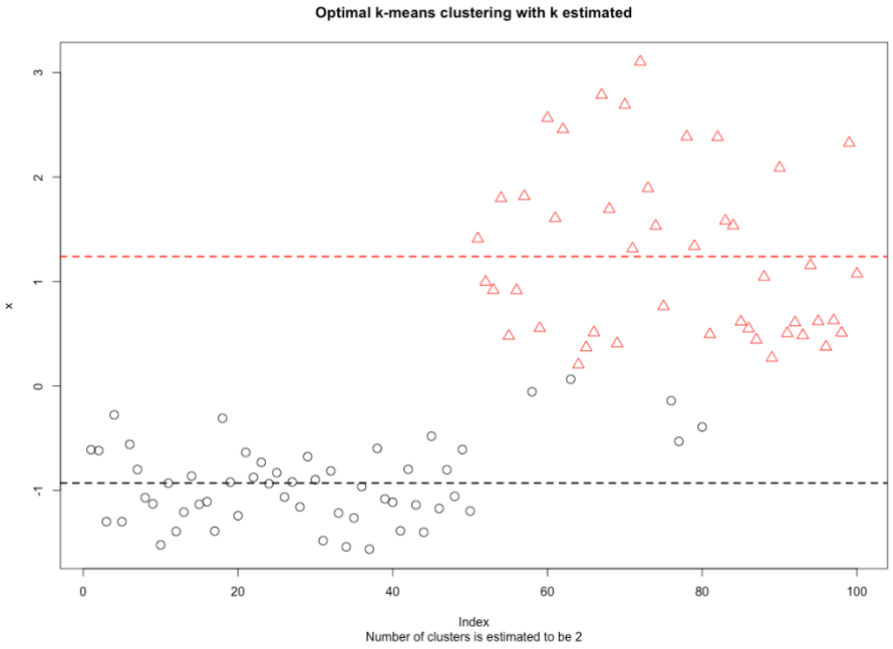


Supplementary Figure 5: Elbow method for 2-solution cluster validation.

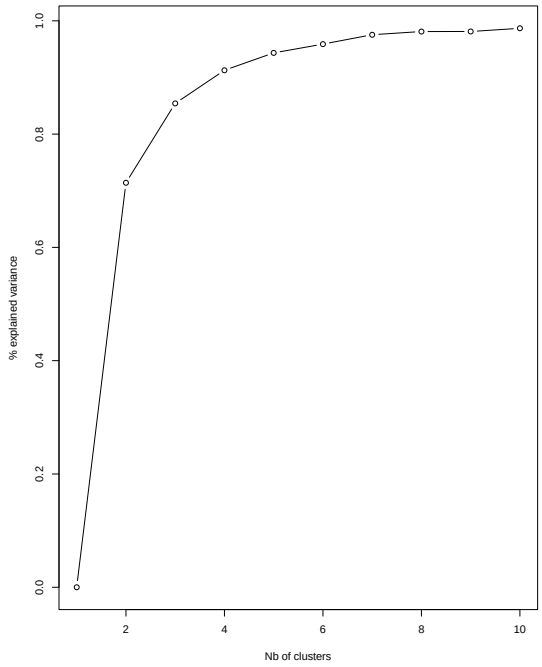


Supplementary Figure 6: Calinski-Harabasz method for 2-solution cluster validation.

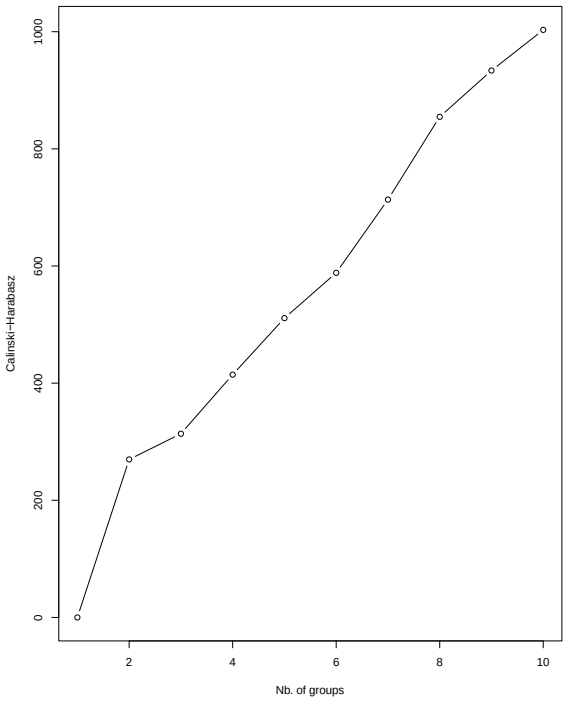
SPQ Negative dimension



Supplementary Figure 7: Two clusters were obtained from applying the ckmeans.1d.dp function on x= SPQ_Negative scores sampled from a Gaussian mixture model estimated with two components. The horizontal axis represents the index number of each point in the data. The dotted lines represent the centers of each cluster.



Supplementary Figure 8: Elbow method for 2-solution cluster validation.



Supplementary Figure 9: Calinski-Haarabasz method for 2-solution cluster validation.

7. Significant results

Schizotypy	Subcortical Structures	Model fitted	Shape *p* value	Intercept *p* value
Negative	R-Pallidum	Linear	*0.000*	*0.000*
	L-Pallidum	Linear	*0.033*	*0.010*
	R-Thalamus	Linear	*0.006*	*x*
Disorganized	R-Hippocampus	Linear	*0.047*	*0.049*
	L-Hippocampus	Linear	*0.048*	*0.023*
	L-Lateral Ventricle	Linear	*x*	*0.025*
	L-Pallidum	Linear	*0.015*	*0.006*

Supplementary Table 2: Differences in longitudinal trajectories between groups**.** Significant values after correction for multiple comparisons with FDR procedure (p <0.05) are displayed in italics.

8. All Results – Group and interaction effects tables

	modelOrder	pValGroup	pValInteraction
LLatVent	1	0.6930062	0.7868281
Lthal	0	0.72983548	0
Lcaud	2	0.3929595	0.52887402
Lput	1	0.94003582	0.84254619
Lpal	1	0.03314157	0.01007911
Lhippo	1	0.17317764	0.06158681
Lamyg	0	0.10236676	0
Laccumb	0	0.85151653	0

Supplementary Table 3: All results for the Negative schizotpy dimension Left hemisphere

modelName	modelOrder	pValGroup	pValInteraction
RLatVent	1	0.61755636	0.555923902
Rthal	0	0.00585552	0
Rcaud	0	0.12521509	0
Rput	0	0.10966843	0
Rpal	1	4.8384E-05	8.54866E-06
Rhippo	1	0.12965536	0.052201439
Ramyg	1	0.71966792	0.797513639
Raccumb	1	0.07993681	0.064689311

modelName	modelOrder	pValGroup	pValInteraction
LLatVent	1	0.053174434	0.024827388
Lthal	0	0.803146363	0
Lcaud	1	0.21501117	0.757191143
Lput	1	0.530961882	0.662854121
Lpal	1	0.014865802	0.006102913
Lhippo	1	0.048692069	0.023369397
Lamyg	0	0.932992589	0

Laccumb	0	0.475167308	0

Supplementary Table 5: All results for Disorganized schizotypy dimension Left hemisphere

modelName	modelOrder	pValGroup	pValInteraction
RLatVent	1	0.88280244	0.6265275
Rthal	0	0.23261714	0
Rcaud	0	0.87980087	0
Rput	0	0.91944943	0
Rpal	1	0.07921889	0.03395813
Rhippo	1	0.04711474	0.04873536
Ramyg	1	0.39406844	0.53136814
Raccumb	1	0.6046945	0.32973924

Supplementary Table 6: All results for Disorganized schizotypy dimension Right hemisphere

modelName	modelOrder	pValGroup	pValInteraction
LLatVent	2	0.1711494	0.08203898
Lthal	0	0.86829365	0

Lcaud	2	0.3873536	0.33868124
Lput	1	0.487973	0.78646833
Lpal	1	0.41915815	0.39541098
Lhippo	0	0.36327616	0
Lamyg	0	0.65176322	0
Laccumb	0	0.81854531	0

Supplementary Table 7: All results for Positive schizotypy dimension Left Hemisphere

modelName	modelOrder	pValGroup	pValInteraction
RLatVent	1	0.324865665	0.204104734
Rthal	0	0.795046989	0
Rcaud	0	0.45203989	0
Rput	0	0.206396741	0
Rpal	1	0.640933101	0.492658396
Rhippo	1	0.091491295	0.06075593
Ramyg	1	0.54230628	0.308545377
Raccumb	1	0.089891893	0.059537298

Supplementary Table 8: All results for Positive schizotypy dimension Right hemisphere

9. Analyses without covariates

Below are presented the results of analyses when covariates were removed. We conducted the same statistical analyses, without Block design and vocabulary subtests and externalized and internalized standardized scores as covariates.

The only covariates present in the models were: ICV and gender.

modelName	modelOrder	pValGroup	pValInteraction
LLatVent	1	0.73602365	0.78405417
Lthal	0	0.52738858	0
Lcaud	2	0.32874811	0.46099866
Lput	1	0.85266517	0.83091104
Lpal	1	0.03775157	0.01394179
Lhippo	1	0.19790374	0.07232988
Lamyg	0	0.09446529	0
Laccumb	0	0.70524313	0

Supplementary Table 9: All results for the Negative schizotpy dimension Left hemisphere

modelName	modelOrder	pValGroup	pValInteraction
RLatVent	1	0.64754762	0.59606367
Rthal	0	0.00160687	0
Rcaud	0	0.10200773	0

Rput	0	0.05290205	0
Rpal	1	7.91E-05	1.39E-05
Rhippo	1	0.11504737	0.0514459
Ramyg	0	0.13913246	0
Raccumb	1	0.07827117	0.06015082

Supplementary Table 10: All results for the Negative schizotpy dimension Right hemisphere

modelName	modelOrder	pValGroup	pValInteraction
LLatVent	1	0.00621918	0.02873312
Lthal	0	0.98400839	0
Lcaud	1	0.1847172	0.59886879
Lput	1	0.49134281	0.50906288
Lpal	1	0.0248582	0.00910719
Lhippo	1	0.04793698	0.02720439
Lamyg	0	0.77139737	0
Laccumb	0	0.40956093	0

Supplementary Table 11: All results for the Disorganized schizotpy dimension Left hemisphere

modelName	modelOrder	pValGroup	pValInteraction
RLatVent	1	0.69137565	0.39197108
Rthal	0	0.09722271	0
Rcaud	0	0.94659842	0
Rput	0	0.79328184	0
Rpal	1	0.14245187	0.04785491
Rhippo	1	0.04811544	0.04497866
Ramyg	0	0.06301019	0
Raccumb	0	0.95079745	0

Supplementary Table 12: All results for the Disorganized schizotpy dimension Right hemisphere

modelName	modelOrder	pValGroup	pValInteraction
LLatVent	1	0.98356906	0.87168449
Lthal	0	0.8671437	0
Lcaud	2	0.41690237	0.38638047
Lput	1	0.6053036	0.78303998
Lpal	1	0.56222818	0.37952837

Lhippo	1	0.65086854	0.45109745
Lamyg	0	0.72747104	0
Laccumb	0	0.89333453	0

Supplementary Table 13: All results for the Positive schizotpy dimension Left hemisphere

modelName	modelOrder	pValGroup	pValInteraction
RLatVent	1	0.35036434	0.22996295
Rthal	0	0.73182984	0
Rcaud	0	0.44457119	0
Rput	0	0.3149105	0
Rpal	1	0.71165122	0.51084682
Rhippo	1	0.14597671	0.08128228
Ramyg	0	0.58921375	0
Raccumb	1	0.1327986	0.05719919

Supplementary Table 14: All results for the Positive schizotpy dimension Right hemisphere

References:

1. Wechsler D. *Wechsler Intelligence Scale for Children WISC-IV technical and interpretive manual*. San Antonio, TX, US: Psychological Corporation; 2003.

2. Wechsler D. Manual of the Wechsler Adult Intelligence Scale—Fourth Edition (WAIS–IV). New York, NY: Psychological Corporation; 1997.

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7. Wang, H. and Song, M. (2011) Ckmeans.1d.dp: optimal *k*-means clustering in one dimension by dynamic programming. *The R Journal* **3**(2), 29—33.

Appendix 5.

Supplementary material – Study 3

Statistics analysis for between age groups comparison:

A. Kruskal-Wallis

	χ^2	df	p	ε^2
SPQ_positive	91.0	2	<.001	0.431
SPQ_negative	54.3	2	<.001	0.258
SPQ_disorganized	48.5	2	<.001	0.230

B. Pairwise comparisons - SPQ_positive

		W	p
Children	Adolescents	11.69	<.001
Children	Adults	-4.34	0.006
Adolescents	Adults	-10.63	<.001

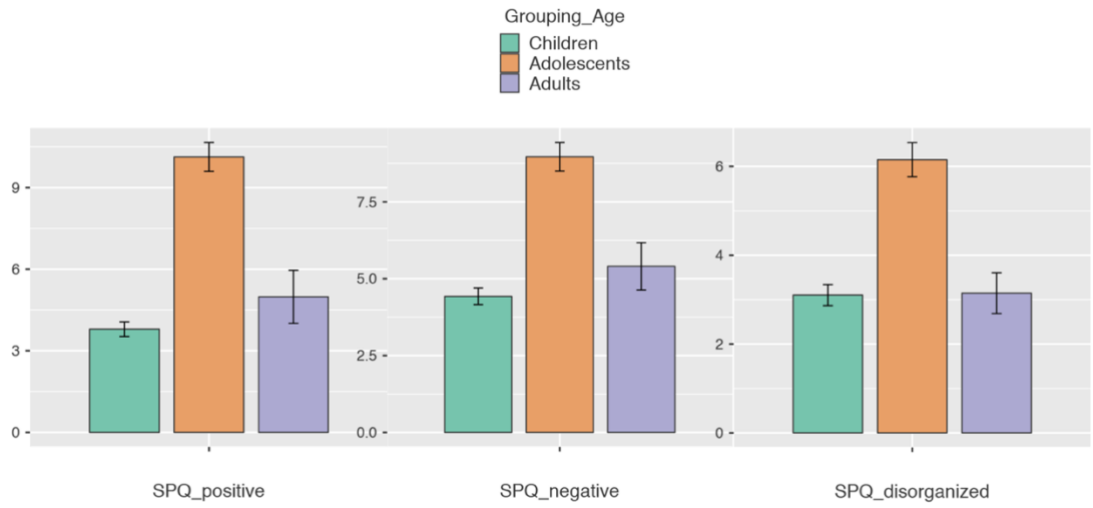
C.Pairwise comparisons - SPQ_disorganized

		W	p
Children	Adolescents	7.50	<.001
Children	Adults	-3.20	0.061
Adolescents	Adults	-8.62	<.001

D. Pairwise comparisons - SPQ_negative

		W	p
Children	Adolescents	9.36	<.001
Children	Adults	-2.54	0.171
Adolescents	Adults	-8.03	<.001

Supplementary Table 1: Children vs Adolescents vs Adults, statistical analyses for schizotypy dimensions.



Supplementary Figure 1: Graphical representation of the three schizotypy dimensions compared per groups Children vs Adolescents vs Adults

Appendix 6.

Supplementary material – Study 5

Description of self-reported instruments

Schizotypy was measured using the Schizotypal Personality Questionnaire (SPQ), which consists of a 74-item, self-report scale, modelled on DSM-III-R criteria for schizotypal personality disorder. Responses are dichotomous (Yes/No) and scattered across 9 subscales collapsing into 3 schizotypy dimensions. The Positive dimension includes magical thinking or odd beliefs, unusual perceptual experiences, ideas of reference and paranoid ideation. The negative dimension assembles excessive social anxiety, constricted affects and absence of close friends. And the disorganised dimension combines odd speech and odd behaviour. Validity and reliability of the SPQ have been widely assessed in non-clinical adolescents and a French version, validated in adolescents, was used in the present study.

The Youth Self-Report (YSR) is a 112-item self-report designed for adolescents (ages 11-17). It assesses behavioural problems and consists in a 3-point scale (*0= not true* to *2= very true*) based on the last 6 months. This questionnaire provides scores on several symptoms scales: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thoughts problems, rule-breaking behaviour and aggressive behaviour. The Adult Self Report (ASR) is a self-report scale, equivalent to the YSR for adults (18-59 y.o), assessing aspects of adaptive functioning and problems. Although it provides scores on the same symptoms scales, this questionnaire additionally asks about tobacco, alcohol and drug use. Both ASR and YSR were validated for francophone samples.

Set up of the MGT

The MGT was conducted in a darkened room, a parcel of which (2 x 3 m) was dedicated to isolate the subject seated in front of a mirror, in between a white wall and a white screen. A large mirror (0.5 x 0.5 m) was disposed on the upper part of a computer desk, held on a tripod, and a keyboard was placed on the lower sliding part of the computer desk. Participants were seated at a distance of 0.4 m in front of the mirror. The room was only illuminated with a halogen light bulb (12V, 20W) mounted on a spotlight and placed 1.2 m behind the participant, with the bulb beam facing the floor. This set-up provided diffuse, indirect lighting over the room, allowing fine facial features to be distinguished in detail whereas colours were attenuated. An experimenter seated behind the screen conducted the MGT. Concerning the recording of the event-related responses, the experimenter explained the use of the keyboard: *"During the 10 minutes while you are looking at yourself in the mirror and staring at your eyes, you may or may not notice changes in your face. If you notice a change then press the button and hold it down for as long as the change lasts. If you do not notice any changes then do not press the button"*. The experimenter made sure the participant understood the instructions and further clarified any ambiguous points before the task began. Trained psychologists (M.D. and D.B.) supervised the process of answering questionnaires to ensure the understanding of the items.

Qualitative assessment Methodology for partition of participants in ASE vs NoASE groups

Two independent raters (M.D and M.D) assessed the qualitative answers of the post mirror task questionnaire in order to reduce bias. The mirror questionnaire was administered in French, but translated in English and provided at the end of the present supplementary material for

clarification. From this questionnaire, we used the 3 following questions for partition of participants in different groups: During the task have you: (1) Noticed a change in light, color or contrast? If yes please describe; (2) Did you see another person in the mirror? If yes, please describe; (3) Please provide a listing of all types of modifications you saw during the task. Both raters were instructed to include participants in one of the two groups based on the most significant illusion they reported. The classification criteria were: (1) the ASE group must include participants who observed another identity, either human or non-human (2) the NoASE group should include participants who experienced changes of light/color/contrast and/or deformation of their own faces**.** As an example, a participant described "My face became black, I only had one eye, it seemed like I was a Zombie", this participant was included in the ASE group based on the fact that he reported seeing a non-human identity. Another participant explained "I saw my face deformed; the light was changing and my face transformed into the face of an old woman", this participant was also included in the ASE group, on the basis of seeing another human facial identity. The second group (NoASE) gathered participants who reported seeing only changes of light/color/contrast or seeing deformation of their own faces. For example, participants reported on the questionnaire: "My cheeks became rounder, my mouth and nose became bigger", "I saw some changes in terms of light (lighter/darker), a laser light (red and white) around me" or "nothing". Both raters agreed on the classification.

It should be noted that the subject classification we used in our study differed from the study by Fonseca-Pedrero *et al* as they separated participants on 4 different groups (1= slight changes of colour/light; 2= deformation of their own faces; 3= other facial ID; 4= non-human vision).

Moreover, participants presenting negative hallucinations, such as own-face disappearance (n=10), were excluded from the NoASE group to ensure the quality of our control group.

Event related responses recorded during the MGT

Four MGT quantitative event-related responses were used in the analyses: first onset, frequency, mean duration and cumulative duration. The first onset variable corresponded to the duration from the beginning of the task until the participant pressed the button for the first time. The frequency was defined as the number of times participants pressed the button**,** averaged per minute. Mean duration translated the mean time they held the button pressed, and cumulative duration; the sum of duration of apparitions averaged per minute. Results of the behavioral analysis of the MGT are presented in table 1.

MRI acquisition and pre-processing

Acquisition

The T1-weighted sequence was collected with a 3D volumetric dimension using the following parameters: TR = 2500 ms, TE = 3 ms, flip angle = 8°, acquisition matrix = 256 x 256, field of view = 22 cm, slice thickness = 1.1 mm, 192 slices. For the rs-fMRI sequence, subjects were asked to keep their eyes open, fixate a cross on the screen, let their thoughts wander and refrain from falling asleep for the duration of the 8-minute scan. Head movement was minimised during scanning with a comfortable vacuum cushion constraint. The 200 blood-oxygenation-level-dependent (BOLD) images were acquired as follow: TR = 2400 ms, TE =30 ms, 38 axial slices, slice thickness = 3.2 mm, flip angle = 85°, acquisition matrix = 94 x 128, field of view = 96 x 128.

fMRI pre-processing

The first 10 functional volumes were discarded to remove T1 signal equilibration effects. Images were corrected for errors in slice timing using the middle slice as reference under descending acquisition, and realigned with respect to the mean image to correct for motion. T1-weighted anatomical image of each subject was co-registered to the mean realigned functional images and segmented in six outputs (gray and white matter, CSF, bones, skin and air). The registration step employed a Diffeomorphic Anatomical Registration using Exponential Lie algebra (DARTEL) to create a population-specific template. The resulting template was then spatially normalised to standard stereotaxic space (based on the Montreal Neurological Institute (MNI) coordinate system). Following normalisation, spatial smoothing was applied using an isotropic Gaussian smoothing kernel with a full width at half maximum (FWHM) of 6mm in order to decrease spatial noise prior to statistical analyses. Finally, to avoid spurious correlations due to non-neural signal, two additional steps were conducted using DPARSF toolbox (http://ffmri.org/DPARSF); the signal was linearly detrended and bandpass filtered (0.01-0.1 Hz) to reduce the effect of low frequency drift and high frequency physiological noise.

Important details for the Independent Component Analysis

Data were reduced through three reduction steps (two PCA and one ICA reduction) and concatenated at each of these stages. The number of independent components was fixed at 20 consistently with the minimum description length estimate. Participants' spatial maps

represented regional strength of functional connectivity, which is defined as statistical correspondence of each voxel to the average network time course. Each set of component maps was transformed into z-scores to centre the distribution's maximum point to the normal curve at zero. ICA method has been proved to be helpful in effectively isolating artefact as distinct independent components, thus the 10 other components were considered as artefacts, either due to motion, or to signal from the ventricles or WM. We used ICA rather than seed-based approaches to identify networks as this data-driven method eliminates the arbitrary choice of seed regions and simultaneously take into account the relationship between all voxels (as opposed to simple pair wise correlations).

Descriptive measures of participants

In our sample, 26,6% (*n=20*) reported only slight changes of light or colour, 33,3% (*n=25*) perceived deformation of their own face, 30,6% (*n=23*) saw another facial identity and 9,3% (*n=7*) had a non-human vision. The ASE group was composed of 30 participants (16 males and 14 females) and the no ASE group of 45 (23 males and 22 females).

Behavioral analysis of participants who did not come back in T2

To ensure the quality of the longitudinal results, we verified whether participants who did not come back for T2, differed from the others on the variables of interest. To do so, we classified participants in two groups: those who came at both time points and those who only participated in the study at T1. We compared the scores, using non-parametric Mann-Whitney U tests for independent samples, on each event related measures of the MGT: mean duration (U=578, p=0.18), first-onset (U=677, p=0.79), frequency (U=632, p=0.46), cumulative duration

(U=558, p=0.12) as well as their scores on the three dimensions of the SPQ: positive (U=572, p=0.08), negative (U=547, p=0.09), and, disorganized (U=517, p=0.06). None of the variables presented statistically significant differences between the two groups. They did not statistically differ in age (U=536, p=0.78) and gender (X^2=0.12, p=0.73) either.

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