DOCTORAL THESIS

Characterising social cognition and neurobiological risk factors for psychosis in a high schizotypy sample
a multimodal approach

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Characterising social cognition and transition-pertinent neural abnormalities in high schizotypy samples, a multidisciplinary approach

by

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Abstract

Introduction

Schizophrenia symptomatology exists on a continuum ranging from subclinical psychotic-like experiences in the general population (schizotypy) to full-blown clinical symptoms. High schizotypy individuals are at an increased risk for developing clinical diagnoses, yet previous work has not investigated key neural abnormalities of schizophrenia in these samples.

Methods

To ensure findings are informative for clinical risk, we only recruited individuals scoring at the extreme low/high end of the Schizotypy Personality Questionnaire. 27 high schizotypy (HS) and 26 low schizotypy (LS) individuals to take part in two functional magnetic resonance imaging (fMRI) tasks assessing social learning. Participants also underwent a resting state fMRI and a magnetic resonance spectroscopy scan.

Results

HS subjects, compared to LS, present with abnormal learning of social information. HS overestimate the volatility of social cues and are slower to learn about global changes in social context. Furthermore, HS subjects show reduced neural activity in the dopaminergic midbrain and increased frontal cortex activity in response to prediction errors during social learning. HS subjects also present with a reduced resting-state functional connectivity between hippocampus and striatum/thalamus and with reduced GABA and Glu metabolite levels in the prefrontal cortex.

Discussion

HS subjects, representing the earliest risk for clinical transition to schizophrenia, already present with key neural abnormalities implicated in progression, mainly abnormal hippocampal functioning and abnormal GABA/Glu levels. These results encourage investigations of HS to facilitate a comprehensive view of risk/protective factors for clinical transition. The results also show that HS subjects already present with abnormal hierarchical learning as seen in clinical samples. HS subjects neutrally underweight prediction errors indicating an improper processing of these learning cues. They also present with compensatory activity in frontal cortex enabling behavioural performance similar to LS. The abnormal learning from social cues could explain not only the social functioning deficits key to schizophrenia, but also other cognitive biases observed in these populations.

Contents

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Chapter One
General Introduction

1.1 Schizophrenia

Schizophrenia is conceptualized as a chronic and persistent neurocognitive disorder that presents with diverse symptomology and heterogeneous levels of severity and functioning (Freedman et al., 2005; Ross, Margolis, Reading, Pletnikov, & Coyle, 2006). The most common symptomatology associated with this condition is the presence of hallucinations and delusions (commonly referred to as positive symptoms), poor planning, reduced motivation, apathy and blunted affect (referred to as negative symptoms), and disorganized communication (Saha, Chant, Welham, & McGrath, 2005). While the incidence of the disorder is relatively low (global point prevalence in 2016 was estimated to be 0.28%), the prevalent cases globally have risen from 13.1 million in 1990 to 20.9 million in 2016, and the condition is one of the major contributors to the global burden of disease (Charlson et al., 2018). Researchers speculate the substantial burden is partly a reflection of three features of schizophrenia: (a) the disorder usually has its onset in early adulthood, (b) despite available treatments, approximately two-thirds of affected individuals have persisting or fluctuating symptoms, and (c) the burden is largely due to deficits in functioning which cannot be treated by antipsychotic medication (Carrión et al., 2013; Saha et al., 2005). Indeed, nearly one third of adult patients who received a schizophrenia diagnosis also experienced a psychotic episode at an earlier point in their life, most commonly before the age of 19 (Mayoral et al., 2008; Wozniak, Block, White, Jensen, & Schulz, 2008). The deficits in functioning reduce independence, lower productivity, limit educational attainment, and decrease quality of life (Fleischhaker et al., 2005). Impairments in social and role functioning are particularly problematic, because patients

consistently have difficulty developing and maintaining many traditional societal roles, such as friend, spouse, parent, student, or worker (Harvey, 2013; Horan, Subotnik, Snyder, & Nuechterlein, 2006; Hutchinson et al., 1999; Nanko & Moridaira, 1993). Even with optimal medication treatment and remission of positive symptoms, functional outcomes are poor during the early years of the illness (Robinson, Woerner, McMeniman, Mendelowitz, & Bilder, 2004; Tohen et al., 2000; Ventura et al., 2011). The literature around first-episode psychosis has suggested a high percentage of relapse rates during the initial phase and years around the onset of symptoms, with an increased risk for relapse in the three years that followed the episode (Chen et al., 2005). Linked to these findings, there has been concerns that the current classification system of the disorder is potentially imposing arbitrary categorical distinctions limiting the capacity to identify relevant neuropsychological and neurobiological markers (Esterberg & Compton, 2009).

Prior to the implementation of the DSM-5, in the DSM-IV, schizophrenia was classified into distinct subtypes (American Psychiatric Association, 2013). Yet, despite numerous studies into the physiological correlates of schizophrenia and related disorders, no biological markers, or endophenotypes have yet been identified (Nelson, Seal, Pantelis, & Phillips, 2013). There is no test (biological or otherwise) that will unequivocally distinguish someone with psychosis, from someone who is psychologically healthy or experiencing another psychiatric illness (Nelson et al., 2013; Wing & Agrawal, 2003; Wong & Van Tol, 2003). This overlap between clinical and non-clinical samples indicates that categorical diagnoses such as that of schizophrenia may obscure the true psychosis phenotype. This could reflect a misrepresentation of latent constructs, and may lead to erroneous diagnoses, inappropriate treatment, and conflicting research findings.

Indeed, there is a growing consensus that dimensional views of schizophrenia and other psychotic disorders may be a more valid representation of the population distribution (Nuevo et al., 2012; Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). Several epidemiologic and clinical studies (Krabbendam, Myin-Germeys, Bak, & Van Os, 2005; Livingston, Kitchen, Manela, Katona, & Copeland, 2001; Lundberg, Cantor-Graae, Kabakyenga, Rukundo, & Östergren, 2004; Wiles et al., 2006) have demonstrated a symptomatic continuum of psychotic like experiences (e.g. delusional and hallucinatory) within the general population, extending from subtle features of psychoticism, to self-reported psychotic symptoms in individuals in the general population, to clinical cases of primary psychotic disorders in mental health care settings (Verdoux & van Os, 2002). Prevalence rates of psychotic-like experiences in the general population vary from around 5-8% in adult samples (Kelleher et al., 2012; Van Os et al., 2009) and around 17% among children and adolescents (Kelleher et al., 2012). Different experiences also have varying prevalence rates, with the most common being hearing voices (median prevalence 13%; Beavan, Read, & Cartwright, 2011) and hallucinations (5.2%; McGrath et al., 2015); with delusional experiences being less common (1.3%; McGrath et al. 2015). Despite the variation in prevalence estimates of psychotic experiences in the general population and in nonpsychiatric clinical samples, which is likely due to differences in study samples, definitions, operationalizations, and the measurement of such experiences, the estimates lend credibility to the notion that psychotic symptoms occur among a much broader segment of the population compared to just those with traditionally defined psychotic disorders. In fact, it has been suggested that paranoid ideation, for example, is nearly as common as symptoms of anxiety and depression in the general population (Freeman et al., 2005; Johns et al., 2004). To illustrate the characteristics of the different levels of psychotic symptomatology, the following sections will describe schizophrenia disorder, populations at clinical high-risk for psychosis and schizotypy traits, i.e.

personality measures considered to represent an underlying vulnerability to developing psychosis.

1.1.1. Schizophrenia characteristics

Schizophrenia is a heterogenous disorder whose symptoms can be parsed into separate domains: positive, negative and disorganised symptoms (APA, 2013). Positive symptoms denote the occurrence of something that would not be present in healthy individuals, such as hallucinations and delusions. Hallucinations are false perceptions, most commonly of auditory nature but can occur in any sensory modality (Fletcher & Frith, 2009). Delusions are persistent bizarre or irrational beliefs that are not easily understood in terms of an individual's social or cultural background (APA, 2013). Positive symptoms contrast with negative symptoms, which are defined by the absence of normal functions, as is the case with reduced speech output (alogia), loss of motivation (avolition), deficits in experiencing pleasure (anhedonia), deficits in seeking social interactions (asociality) and deficits in expressing emotions (Andreasen, 1982; Buchanan, 2007).

Beyond these symptom clusters, evidence from hundreds of studies and thousands of individuals concludes that schizophrenia is associated with impairment across a wide range of higher-order cognitive performance domains (Schaefer, Giangrande, Weinberger, & Dickinson, 2013). This is of particular importance, as cognitive dysfunction is an important predictor of occupational and functional impairments observed in people with this disorder (Bora, Yücel, & Pantelis, 2009a; Bora, Yücel, & Pantelis, 2010; Green, Michael Foster, Kern, Braff, & Mintz, 2000; Heinrichs & Zakzanis, 1998; Liddle, 2000). Studies have provided remarkably consistent evidence that schizophrenia involves a broad impairment in cognitive function on the order of 1.0–1.75 standard deviations below the normal mean, with some

variability in the extent of impairment across cognitive domains (Censits, Ragland, Gur, & Gur, 1997; Heaton et al., 2001; Mohamed, Paulsen, O'Leary, Arndt, & Andreasen, 1999). Although some reviews highlight particularly large cognitive deficits in the domains of verbal episodic memory (Heinrichs & Zakzanis, 1998; Reichenberg, & Harvey, 2007; Simonsen et al., 2009), executive functioning (Reichenberg & Harvey, 2007), or processing speed (Dickinson, Ramsey, & Gold, 2007; Simonsen et al., 2009), the most consistent finding across studies has been an overall, generalized impairment across neuropsychological measures that persists in every clinical state and across patients' lifespans (Albus et al., 2002; Hill, Schuepbach, Herbener, Keshavan, & Sweeney, 2004; Hughes et al., 2003; Hyde et al., 1994).

Chronicity, severity of symptoms, comorbidity, as well as medication status and dosage act as possible moderators of cognitive performance in schizophrenia populations (Dibben, Rice, Laws, & McKenna, 2009). Negative symptoms and disorganization appear to be correlated with deficits in executive functions as well as with impaired intellectual functioning in schizophrenia (Dibben et al., 2009; Nieuwenstein, Aleman, & de Haan, 2001). With regard to the age of illness onset, there is some evidence that early onset, as compared to individuals with an adult-onset of schizophrenia, is associated with greater severity of cognitive impairment, namely larger deficits in IQ, executive functioning, psychomotor speed, and verbal memory (Rajji, Ismail, & Mulsant, 2009). Longer duration of untreated psychosis has been linked to worse cognitive function (Scully, Coakley, Kinsella, & Waddington, 1997), suggesting that intervention close to the onset of psychosis is required to reduce the cognitive deficit and its subsequent impact on quality of life. Early intervention is known to reduce positive and negative symptoms (Petersen et al., 2005), to significantly reduce the risk of relapse and the number of hospital admissions (Bark et al., 2003) and it has positive effects on social and occupational functioning (Craig et al., 2004; Marshall, & Rathbone, 2011).

Finally, neuroimaging studies have consistently reported differences between healthy controls and patients with schizophrenia in both structural, functional and neurochemical investigations. Results from the largest cooperative analysis to date of brain Magnetic Resonance Imaging (MRI) scans from individuals with schizophrenia have concluded that patients present with significantly smaller volumes of hippocampus, amygdala, thalamus and accumbens (van Erp et al., 2016). The findings also indicate patients, compared to healthy controls, have significantly larger pallidum and lateral ventricle volumes, and these were associated with duration of illness and age (van Erp et al., 2016). Voxel-based Morphometry (VBM) studies have also consistently reported gray matter deficits in schizophrenia, especially in the frontal and temporal lobe, cingulate and insular cortex and the thalamus (Ellison-Wright, Glahn, Laird, Thelen, & Bullmore, 2008; Ellison-Wright & Bullmore, 2010; Fornito, Yücel, Patti, Wood, & Pantelis, 2009; Glahn et al., 2008). Abnormal functional activity is also well-established in patients with schizophrenia, with abnormal activation during verbal memory tasks (Heckers et al., 1998; Ragland et al., 2004; Yurgelun-Todd et al., 1996), episodic memory tasks (Danion et al., 2005; Hannula et al., 2010; Titone, Ditman, Holzman, Eichenbaum, & Levy, 2004; van Erp et al., 2008) and higher order cognitive tasks assessing flexibility in thinking, abstract concept formation and the ability to shift or maintain attentional set (Holmes et al., 2005; Orellana, & Slachevsky, 2013; Volz et al., 1997; Weinberger et al., 1996). These studies consistently report abnormal functional activity in frontal (inferior, superior, dorsolateral prefrontal cortex) and temporal regions (hippocampus, superior temporal gyrus, middle temporal gyrus) in patients.

Atypical patterns of functional connectivity during resting state have also been identified in schizophrenia, with studies reporting hypoactivation in the ventromedial prefrontal cortex, hippocampus, posterior cingulate cortex and precuneus (Kühn & Gallinat, 2011). Patients with schizophrenia consistently display reduced connectivity within and

between brain networks involved in internally oriented attention and self-referential processes (default mode network), processing of emotion (affective network), salience (ventral attention network), gating information (thalamus network), goal-directed regulation of these functions (frontoparietal functions) and auditory processing (somatosensory network; (Dong, Wang, Chang, Luo, & Yao, 2017).

The progressive brain changes observed in schizophrenia, particularly the loss of brain tissue, may represent an ongoing pathophysiological process, with one possible mechanism being a dysfunction of the glutamatergic system (Harrison & Weinberger, 2005). Indeed, meta analytical studies have consistently reported that medial frontal region glutamate (main excitatory neurotransmitter) is decreased, and glutamine is increased in patients with schizophrenia as compared with healthy individuals (Marsman et al., 2011). The aberrant glutamate levels, indicative of a glutamatergic system dysfunction, are implicated as a possible origin of the decreased brain volumes observed in patients with schizophrenia (Marsman et al., 2011). Group-by-age associations revealed that in patients with schizophrenia, glutamate and glutamine concentrations decreased at a faster rate with age as compared to healthy controls (Marsman et al., 2011). Significantly lower levels of gamma-Aminobutyric acid (GABA; main inhibitory neurotransmitter) have also been identified in the prefrontal cortex in patients with schizophrenia as compared to healthy controls, and the lower levels have been associated with lower levels of general cognitive functioning (Marsman et al., 2014). A full review of the abnormal neurobiology in schizophrenia, and its significance for symptomatology, is beyond the scope of this work, but this brief summary provides for a relevant comparison point between chronic schizophrenia and prodromal conditions.

1.1.2. Clinical high-risk populations (CHR)

During the past decade, a well-defined set of clinical criteria have been developed to identify young people with a clinical high risk for psychosis (Pukrop et al., 2007; Yung et al., 2005). The clinical high-risk (CHR) criteria designates help-seeking young people (aged between 14 and 30) who meet the criteria for 1 or more of the following: (1) Attenuated psychotic symptoms: people who have experiencing subthreshold, positive psychotic symptoms during the past year; (2) a brief limited intermittent psychotic symptom (commonly referred to as BLIPS): people who have experienced episodes of frank psychotic symptoms that have not lasted longer than a week and have spontaneously abated (without treatment); and (3) the trait and state risk factors: those with a first-degree relative with a psychotic disorder or the identified patient has an schizotypal personality disorder in addition to a significant decrease in functioning or chronic low functioning during previous year (Yung, & Nelson, 2013; Yung et al., 2003; Yung, Phillips, Yuen, & McGorry, 2004). Across studies, severity of attenuated positive symptoms, poorer social functioning, substance abuse, and genetic risk for schizophrenia appear to be consistent predictors of conversion to psychosis (Fusar-Poli et al., 2012; Gee, & Cannon, 2011). The CHR state indicates a very high risk of transitioning to a first episode psychosis within the first 2 years of clinical presentation, and this risk progressively increases across this period (Fusar-Poli et al., 2012). Although reported transition rates vary, the best powered studies have observed rates of conversion to full psychosis of about 15-29% over 2–3 years of follow-up (Fusar-Poli & Schultze-Lutter, 2016; Kempton, Bonoldi, Valmaggia, McGuire, & Fusar-Poli, 2015). Early identification and treatment of subjects at CHR for psychosis may result in attenuation, delay or even prevention of the onset of first psychosis in some individuals (Correll, Hauser, Auther, & Cornblatt, 2010; Yung et al., 2005; Yung et al., 2006).

A number of studies have provided evidence indicating that the cognitive and intellectual deficits characteristic of schizophrenia are evident before the onset of psychosis

(Bora et al., 2010; De Herdt et al., 2013; Giuliano, Li, Mesholam-Gately, Sorenson, Woodberry, & Seidman, 2012; Lencz et al., 2006; MacCabe, 2008; Reichenberg et al., 2010; Woodberry, Giuliano, & Seidman, 2008). Cognitive deficits in CHR groups have generally been shown to be intermediate between healthy control groups and first-episode psychosis samples, with small-to-medium impairments across most neurocognitive domains (Fusar-Poli, Deste et al., 2012; Giuliano, Li, Mesholam-Gately, Sorenson, Woodberry, & Seidman, 2012). Findings from CHR cohort studies suggest that certain cognitive impairments in these individuals might indicate stable vulnerability markers (sustained attention; Francey et al., 2005; Lencz et al., 2006), while others (verbal IQ, processing speed, verbal memory, working memory) might predict transition to first psychosis (Brewer et al., 2005; Jahshan, Heaton, Golshan, & Cadenhead, 2010; Lencz et al., 2006; Pukrop et al., 2007; Seidman et al., 2010). In addition, lower neurocognitive performance has been associated with poorer social and role functioning in CHR samples, with neurocognitive performance and functioning at baseline being key predictors of long-term functioning in those who do and do not convert to full-blown psychosis (Carrion et al., 2013).

A growing body of evidence suggests early neurodevelopmental brain changes preceding psychosis can be detected in CHR samples. A large volumetric MRI study in a CHR population aged 20 years, compared to healthy age-matched controls, reported smaller whole brain volume in CHR individuals (Velakoulis et al., 2006). Several VBM studies have shown changes in both gray (Borgwardt, McGuire, Fusar-Poli, Radue, & Riecher-Rössler, 2008; Borgwardt et al., 2007; Meisenzahl et al., 2008; Pantelis et al., 2003) and white matter (Walterfang et al., 2008; Witthaus et al., 2008) clusters in young adults (20–25 years) at CHR, predominantly in prefrontal and temporal lobe areas. Several authors have shown that young, healthy individuals with a positive familial history for psychotic disorders show subtle neuroanatomical alterations in the hippocampus, the anterior cingulate cortex and the prefrontal

cortex, possibly as a result of early neurodevelopmental disturbances (Job et al., 2003; Lawrie et al., 1999; Yücel et al., 2003). The most prominent alterations in brain structure have been identified bilaterally in gray matter volume reductions covering the medial and lateral prefrontal cortex and the anterior cingulate cortex (Job et al., 2003; Meisenzahl et al., 2008; Pantelis et al., 2003) and the hippocampus (Borgwardt, et al., 2007). Findings from prospective and longitudinal MRI studies comparing patients who did and did not subsequently develop psychosis suggest additional alterations in the inferior temporal and limbic regions in the converter group (Borgwardt et al., 2007; Pantelis et al., 2003). Transition to psychosis may be associated with further structural brain changes within the left hemisphere, including the orbitofrontal region and the anterior cingulate, the parahippocampus, and the inferior temporal regions (Job et al., 2003; Pantelis et al., 2003). These structural changes are consistent with studies of first-episode patients (Steen, Mull, Mcclure, Hamer, & Lieberman, 2006; Vita, De Peri, Silenzi, & Dieci, 2006). Similar abnormalities in the hippocampus, anterior cingulate cortex and prefrontal cortex have been reported in young, healthy individuals with a positive familial history of psychotic disorders (Lawrie et al., 1999; Yücel et al., 2003).

These volumetrically reduced regions in both CHR and schizophrenia populations can be engaged by specific cognitive paradigms, the most commonly used ones being working and verbal memory, and social cognition tasks (Fusar-Poli et al., 2012). In line with the findings of CHR status being associated with widespread impairments in executive functions including social processing, memory and attention (Fusar-Poli et al., 2012), recent reviews have found consistent evidence for abnormal (higher and lower) prefrontal (superior, inferior, medial, or orbito frontal gyrus) activation in CHR compared to healthy controls (Dutt et al., 2015; McGorry, Killackey, & Yung, 2007; Smieskova et al., 2013; Sridharan, Levitin, & Menon, 2008; Venkatasubramanian, Puthumana, Jayakumar, & Gangadhar, 2010). Cortical activation has also been linked to functional outcome, with CHR subjects showing

greater cortical activation associated with poor functional outcome at follow-up (Allen et al., 2015). Moreover, CHR individuals who later develop psychosis showed increased activation in bilateral prefrontal cortex (Allen et al., 2012). These findings suggest that prefrontal function begins to decline before the onset of clinical illness and may represent a vulnerability marker in assessing the risk of developing psychosis (Morey et al., 2005). Altered resting state functional connectivity has also been observed in CHR populations. The well-established functional connectivity abnormalities of the thalamus and temporal areas observed in schizophrenia are also present in the CHR period, with aberrant connectivity of the temporal cortex most associated with psychosis risk (Colibazzi et al., 2017; Giraldo-Chica & Woodward, 2017). CHR subjects also exhibit hyperconnectivity within default mode network regions (Liu et al., 2010; Shim et al., 2010), similarly to findings in clinical schizophrenia research (Bluhm et al., 2007; Whitfield-Gabrieli et al., 2009; Zhou et al., 2007).

Altered brain glutamatergic transmission has also been implicated in CHR samples (Bossong et al., 2019; Egerton et al., 2014; Stone et al., 2009). Adverse clinical outcomes in these individuals are associated with increases in hippocampal glutamate levels and follow-up assessments indicate that increased glutamate levels are associated with low level of functioning (Bossong et al., 2019). Moreover, subsequent onset of psychosis has been associated with higher baseline levels of glutamate (Bossong et al., 2019). Increased hippocampal glutamate levels also distinguish CHR who transition to psychosis and are not characteristic of total CHR cohort assessments (Bossong et al., 2019), suggesting the glutamatergic system dysfunction is predictive of transition to psychosis. Regions beyond the hippocampus also show abnormal glutamate levels, de la Fuente Sandoval demonstrated increased baseline glutamate levels in the striatum of clinical high-risk individuals who developed a first episode of psychosis (de la Fuente-Sandoval et al., 2013). Allen and colleagues found that a poor functional outcome in clinical high-risk individuals was linked to

lower glutamate concentrations in the thalamus at baseline (Allen et al., 2015), whereas Egerton reported that lower thalamic glutamate levels were associated with a failure to achieve symptomatic remission from the clinical high-risk state (Egerton et al., 2014). Aberrant levels of glutamate in prefrontal regions has also been reported in CHR samples (Egerton et al., 2014; Stone et al., 2009). Animal models provide support for these findings, as ketamine and phencyclidine (N-methyl-D-aspartate drugs inducing effects resembling the positive and negative symptoms of schizophrenia) have been shown to cause an increase in glutamate release specifically in the prefrontal cortex (Lorrain, Baccei, Bristow, Anderson, & Varney, 2003; Moghaddam, Adams, Verma, & Daly, 1997). This abnormal glutamate release is linked to toxic changed in cortical neurons (Olney & Farber, 1995; Sharp, Tomitaka, Bernaudin, & Tomitaka, 2001). Correspondingly to the reduced glutamate in clinical schizophrenia, a study reported that prefrontal cortex glutamate levels are lower in both twins with schizophrenia and in their unaffected twins compared with in healthy controls, suggesting that prefrontal cortical glutamate reductions may represent markers of schizophrenia risk (Lutkenhoff et al., 2010). Furthermore, abnormal cortical GABA levels have been observed in CHR samples as well (de la Fuente-Sandoval et al., 2015; Menschikov et al., 2016), and these have been inversely correlated with the severity of negative symptoms (Modinos, Gemma, Şimşek et al., 2017). Noteworthy, findings from unaffected siblings of patients suggest lower cortical GABA levels compared to healthy controls signifying that prefrontal cortical GABA reductions may represent another marker of schizophrenia risk (Marenco et al., 2016).

1.1.3. Schizotypy

Schizotypy describes a cluster of personality traits that include odd or bizarre behaviour, strange speech, magical thinking, unusual perceptual experiences, and social anhedonia (Nelson et. al., 2013). There is some disagreement regarding the underlying factor structure of schizotypy (Fonseca-Pedrero, Paino, Lemos-Giráldez, Sierra-Baigrie, & Muñiz, 2011; Mason & Claridge, 2006; Stefanis et al., 2004). However, the prevailing understanding is that it is comprised of three identifiable factors, which broadly correspond to the positive, negative and disorganised dimensions of schizophrenia (Fonseca-Pedrero et al., 2011; Wuthrich, & Bates, 2006). The first factor is the 'cognitive-perceptual factor', which includes magical thinking, unusual perceptual experiences, ideas of reference and paranoia (Raine, 1991; Raine, 2006). The second is the 'interpersonal factor', mapping to negative symptoms, which includes constricted affect, social anxiety, lack of close personal relationships, and suspiciousness (Raine, 1991; Raine, 2006). The final 'disorganised factor' includes odd behaviour and odd speech (Raine, 1991; Raine, 2006). Schizotypy is associated with heightened risk for the development of psychotic disorder compared to the general population, with studies estimating that around 2% of these individuals meet criteria for a schizophrenia-spectrum diagnosis at a 10-year follow-up (Kwapil, Gross, Silvia, & Barrantes-Vidal, 2013; Poulton et al., 2000). Assessment of schizotypy provides a valuable first stage for identifying individuals possessing liability to psychosis prior to the appearance of clinical manifestations. This should facilitate the study of developmental pathways to psychosis and, perhaps as importantly, the identification of protective factors in individuals not presenting with typical confounding variables associated with schizophrenia spectrum disorders (i.e. medication, comorbidity).

A popular model of the potential relationship between schizotypal personality traits and schizophrenia is the fully dimensional approach, which is outlined by Claridge and colleagues (Claridge & Beech, 1995; Claridge & Davis, 2013; Rawlings, Williams, Haslam, & Claridge,

2008). The fully dimensional approach posits that schizotypy represents natural symptom variations present in the general population, which at the extreme of the continuum manifest as vulnerability to mental illness (Rawlings et al., 2008). The main contention advocated by the fully dimensional approach is that the latent structure of schizotypy is on a continuum applying to all members of the population. It is considered to range from low schizotypy and psychological health, to extremely high schizotypy and increased risk for potential dysfunction in the form of psychosis or other disorders from the schizophrenia-spectrum (Claridge & Beech, 1995). The fully dimensional approach is consistent with the majority of current theories pertaining to schizophrenia, which tend to describe continuity between clinical and non-clinical psychosis populations (Linscott & van Os, 2010). Further evidence for the dimensional approach is based on analyses supporting the three-factor structure of schizotypy (cognitive-perceptual, interpersonal and disorganised), which is analogous to the three factor structure of psychosis (positive, negative and disorganised; Liddle, 1987; Rossi & Daneluzzo, 2002; Wuthrich & Bates, 2006). There is also evidence that individuals with psychotic disorders tend to score highly on measures of schizotypy (Camisa et al., 2005; Lenzenweger, 1994).

Regarding cognition, studies have shown that higher levels of schizotypy are associated with impairments in working memory (Kerns & Becker, 2008; Koychev, El-Deredy, Haenschel, & Deakin, 2010; Matheson & Langdon, 2008; Park, Holzman, & Lenzenweger, 1995; Park & McTigue, 1997; Tallent & Gooding, 1999) and in executive functions (Cappe, Herzog, Herzig, Brand, & Mohr, 2012; Gooding, Kwapil, & Tallent, 1999; Park et al., 1995; Raine, Sheard, Reynolds, & Lencz, 1992). Similarly to patients, high schizotypy is associated with impaired verbal fluency (Cochrane, Petch, & Pickering, 2012), impaired early sensorimotor filtering (Kumari, Toone, & Gray, 1997; Kumari, Antonova, & Geyer, 2008; Swerdlow, Filion, Geyer, & Braff, 1995; Takahashi et al., 2010) and impaired visual backward

masking (Cappe et al., 2012). Abnormalities in attention (Bedwell, Kamath, & Baksh, 2006; Bergida & Lenzenweger, 2006), latent inhibition (Kumari & Ettinger, 2010) and in the flexible adaptation of behavioural control following cognitive conflict (Völter et al., 2012) have also been reported. Altered response to emotional stimuli is also characteristic of high schizotypy, with impairments in the recognition and naming of emotional facial expressions (Brown & Cohen, 2010; Germine & Hooker, 2011), in perspective taking (Langdon & Coltheart, 2001; Arzy, Mohr, Michel, & Blanke, 2007) and in Theory of Mind (Morrison, Brown, & Cohen, 2013). The deficits observed on these tasks are generally similar in kind to those observed in schizophrenia. Furthermore, at least one study has explicitly evaluated neurocognitive functioning in both schizotypy and schizophrenia together, on the basis of a fully dimensional model (Cochrane, Petch, & Pickering, 2012). Cochrane (2012) conducted two separate studies. In the first, it was reported that in non-clinical sample, the Interpersonal (negative) factor of the Schizotypy Personality Questionnaire was related to reduced verbal fluency, and the Disorganised factor was related to reduced negative priming. In the second study, corresponding symptom measures from the Scales for the Assessment of Positive and Negative Symptoms (Andreasen, 1984; Andreasen, 1982; Andreasen, 1989) showed similar relationships with verbal fluency and negative priming in participants with a diagnosis of schizophrenia. Again, similarly to outcomes of research focused on psychosis, relative cognitive deficits associated with schizotypy appear to relate to negative (interpersonal) and disorganised traits rather than positive (cognitive-perceptual) traits (Chen, Hsiao, & Lin, 1997; Moritz, Andresen, Naber, Krausz, & Probsthein, 1999; Park & McTigue, 1997). Of importance in this context is the observation that some of these neurocognitive deficits survive statistical correction for factors such as intelligence (Cochrane et al., 2012; Völter et al., 2012) and neuroticism (Ettinger et al., 2005; Völter et al., 2012), providing further support for the existence of genuine cognitive impairments in people with high levels of schizotypy, over and

above measures of general (cognitive or emotional) functioning. A point of departure in neurocognitive findings is that significant reductions in cognitive measures in people with schizophrenia are often reported alongside medium to large effect sizes (e.g. Reichenberg & Harvey, 2007; Simonsen et al., 2009), whilst effect sizes in studies of schizotypy are often small (e.g. Chen et al., 1997; Noguchi, Hori, & Kunugi, 2008). This may indicate that cognitive decline is more prominent for people with schizophrenia, and indeed may be a significant defining feature of clinical psychosis (Bora, Yücel, & Pantelis, 2010).

Research has indicated that both schizophrenia and schizotypy have been associated with a number of similar neuroanatomical abnormalities. Importantly, several of the key neuroanatomical findings relating to schizophrenia have also been replicated in schizotypy research. Studies have reported that higher schizotypy scores are associated with reduced gray matter volume in medial prefrontal and temporal areas including orbitofrontal cortex, anterior cingulate cortex and superior temporal gyrus (Ettinger et al., 2012; Kühn, Schubert, & Gallinat, 2012; Raine et. al., 1992). While these findings accord well with volume reductions in schizophrenia confirmed by meta-analysis (Glahn et al., 2008), other papers have reported evidence of a positive relationship between psychometric schizotypy levels and temporal and frontal lobe gray matter density in high-risk individuals before conversion to schizophrenia (Kühn et al., 2012; Lymer et al., 2006) and between higher positive psychometric schizotypy and larger global gray matter volumes (Modinos et al., 2010). Of note, large worldwide cooperative meta-analyses of schizotypy psychometric measures show both divergent and consistent results with clinical presentations. Meta-analyses of subcortical brain volumes in schizotypy individuals reported that high schizotypy is associated with smaller nucleus accumbens, a result consistent with schizophrenia and suggesting that these effects are not secondary to disease chronicity or medication but a marker of the psychosis continuum (Antoniades et al., 2019). The same group has reported that schizotypy scores are positively

correlated with mean cortical thickness of frontal pole and orbitofrontal regions, a result opposite to that observed in patients (i.e. thinner cortex; (Antoniades et al., 2020; Kirschner et al., 2020). The early neuroanatomical changes may reflect early microstructural deficits (i.e. in myelination) or may reflect mechanisms of resilience in these samples (Antoniades et al., 2020). It has been speculated that such neuroanatomical changes in full-blown schizophrenia may reflect pathophysiological processes that do not covary with schizotypy in the healthy population but become expressed in the presence of additional risk factors or active pathophysiological (disease) processes (Ettinger et al., 2012; Modinos et al., 2010).

Similarities between neural activation patterns in schizophrenia and schizotypy have been consistently reported. Lower activity has been observed in the striatum during unexpected "prediction error" trials in individuals with higher schizotypy scores (prediction errors defined as a difference between expected/prior expectation and reality; Corlett & Fletcher, 2012), mirroring data from earlier investigations of the prediction error effect in schizophrenia (Corlett et al., 2007). Studies investigating the neural alterations underlying the pursuit deficit in schizotypy have observed a relationship between higher schizotypy scores and lower neuronal response in occipital areas that are known to be associated with early sensory and attentional processing, and motion processing (Meyhöfer et al., 2015), with results being compatible to findings in patients with schizophrenia (Lencer, Nagel, Sprenger, Heide, & Binkofski, 2005; Levy, Sereno, Gooding, & O'Driscoll, 2010). As in schizophrenia and CHR populations, schizotypy is associated with abnormal neural response during cognitive (Ettinger, Meyhofer, Steffens, Wagner, & Koutsouleris, 2014) and during emotional processing (Ettinger et al. 2018). A series of studies in healthy student with high psychometrically measured schizotypy scores also showed increased activation in prefrontal areas during a ToM task despite unimpaired behavioral performance (Modinos, Renken, Shamay-Tsoory, Ormel, & Aleman, 2010). High schizotypy individuals also display reduced prefrontal control of emotional

processing (Modinos, Ormel, & Aleman, 2010) and altered activation patterns during the processing of self-related stimuli (Modinos, Renken, Ormel, & Aleman, 2011) suggesting of abnormal neural processing of emotional stimuli. High positive schizotypy scorers, compared to low positive scorers, showed reduced left dorsolateral prefrontal cortex and elevated right activation in the same region while performing an emotional Stroop task (Mohanty et al., 2005). They also showed abnormal activity in ventral limbic areas, including decreased activity in nucleus accumbens and increased activity in hippocampus and amygdala, areas known to be affected in schizophrenia as well (Mohanty et al., 2005). Summing up, these studies suggest that psychometric schizotypy is associated with certain neuronal mechanisms that were activated by tasks established as neurocognitive markers of schizophrenia (Aichert, Williams, Möller, Kumari, & Ettinger, 2012).

A limited number of studies have investigated resting state connectivity and neurochemistry in schizotypy samples. In line with studies reporting both higher and lower resting state connectivity of striatal regions in patients with schizophrenia (Dandash et al., 2014; Fornito et al., 2013), higher schizotypy scores have been associated with widespread alterations in striatocortical resting functional connectivity (Rössler et al., 2019; Wang et al., 2016). More specifically, increasing schizotypy scores have been associated with greater resting functional connectivity between ventral striatum and dorsolateral prefrontal cortex (Wang, Ettinger, Meindl, & Chan, 2018). Yet, individuals scoring high only on the positive dimension of schizotypy have been shown to present with lower resting state connectivity between striatum and ventromedial prefrontal cortex (Waltmann et al., 2019). Research investigating GABA and glutamate in high schizotypy samples is also limited. The one previous study investigating glutamate levels in individuals scoring high on the positive schizotypy scale only, in comparison to low positive schizotypy, reported no differences in glutamate levels between the groups in the anterior cingulate cortex, but there was an

interaction effects such that glutamate levels were negatively associated with the degree of activation to emotional pictures in the striatum and the medial prefrontal cortex (Modinos et al., 2017). These preliminary findings suggest that cortical glutamate levels might be impaired in high (positive) schizotypes, yet to date there is no direct investigation of this hypothesis in total high schizotypy across all three subfactors.

1.2. Social cognition in schizophrenia

While schizophrenia is associated widespread cognitive impairments, recent work has highlighted that deficits in social functioning are prominent. Indeed, not only are social functioning defining a feature of schizophrenia but are of key importance in terms of functional and clinical outcomes in patients (Bellack, Morrison, Wixted, & Mueser, 1990). Social cognition refers to the psychological processes that are involved in the perception, encoding, storage, retrieval and regulation of information about other people and ourselves (Adolphs, 2001). In other words, social cognition refers to the mental operations underlying social interactions (Brothers, 2002). These processes include social cue perception, experience sharing, inferring other people's thoughts and emotions, and managing emotional reactions to others (Green, Horan, & Lee, 2015).

It needs to be noted that while general cognition and social cognition are related concepts (e.g. both involve working memory capacity), they are classified as different constructs (Penn, Sanna, & Roberts, 2008). Empirically, studies using statistical modeling techniques (Allen, Strauss, Donohue, & van Kammen, 2007; Sergi et al., 2007) and matched task designs (Brunet, Sarfati, Hardy-Baylé, & Decety, 2003; Cutting & Murphy, 1990) have concluded that social cognition is best understood as related to, but distinct from, neurocognition. Conceptually, social cognition involves the interface of emotional and

cognitive processing, whereas neurocognitive processing is relatively affect-neutral (Adolphs, 2003a; Brothers & Ring, 1992). This distinction is also observed at the neural level because activation circuitry associated with social cognition is relatively independent from brain networks involved in executive and other cognitive functions (Adolphs, 2003a; Blakemore & Frith, 2004; Pinkham, Penn, Perkins, & Lieberman, 2003). More specifically, research examining the neural underpinnings of neurocognitive and social cognitive abilities suggest semi-independent systems for processing nonsocial and social stimuli (Adolphs 2003b; Blakemore & Frith, 2004; Bozikas, Kosmidis, Anezoulaki, Giannakou, & Karavatos, 2004; Lee, Farrow, Spence, & Woodruff, 2004; Phillips, Drevets, Rauch, & Lane, 2003; Pinkham et al., 2003). Both systems make substantial demands on brain regions responsible for cognitive domains (such as episodic memory), but social cognition is additionally associated with brain regions responsible for emotional and motivational processing (Adolphs, 2009). Further,, there appears to be only a modest association between neurocognition and social cognition task performance (Kee, Kern, & Green, 1998; Kohler, Bilker, Hagendoorn, Gur & Gur, 2000; Penn et al., 1993; Pinkham, Gur, & Gur, 2007; Sachs, Steger-Wuchse, Kryspin-Exner, Gur, & Katschnig, 2004; Silver & Shlomo, 2001).

Extending this line of research into functional outcomes in schizophrenia, research has shown that social cognition either serves as a mediator between neurocognition and functional status (Addington, Saeedi, & Addington, 2006; Sergi, Rassovsky, Nuechterlein, & Green, 2006; Vauth, Rüsch, Wirtz, & Corrigan, 2004) or it has a direct relationship with functional outcomes such as community functioning and social relationships (Brekke, Hoe, Long, & Green, 2007; Couture, Penn, & Roberts, 2006). Thus, social cognition contributes to functional outcome in schizophrenia in a way that is independent of neurocognition. Furthermore, impaired social functioning also impacts quality of life (Penn et al., 2008) and predicts outcome in schizophrenia, including relapse, poor illness course, and unemployment (Perlick, Stastny,

Mattis, & Teresi, 1992; Sullivan, Marder, Liberman, Donahoe, & Mintz, 1990; Tien & Eaton, 1992).

Researchers speculate that the association between social cognition and functional outcome is related to the ability to quickly process social stimuli and that this process is essential for social interactions. Problems in this area can impact peer, romantic, and family relationships as well as educational and occupational behavior (Couture et al., 2006). In addition, social cognition deficits may impact on independent living skills because the ability accurately assess social cues in the environment (such as someone responding to body odor by increasing bodily distance or making a facial expression of disgust; Couture et al., 2006). Indeed, individuals with schizophrenia often display marked impairments in processing social information, which can result in misinterpretations of the social intent of others, social withdrawal and impaired daily social functioning (Fett, Viechtbauer, Penn, van Os, & Krabbendam, 2011; Green, Hellemann, Horan, Lee, & Wynn, 2012). In such individuals, social cognitive impairment has a more-negative effect on daily functioning than non-social cognitive impairment (Fett et al., 2011; Green et al., 2012). Finally, a number of studies using self-report measures have shown that individuals with schizophrenia use cognitive reappraisal (strategies to regulate emotions, which influences how emotion is experienced, when it is experienced and how it is expressed) less frequently than do healthy individuals, and that lower use of this process is associated with poor outcomes in community functioning and more severe clinical symptoms (Henry, Rendell, Green, McDonald, & O'Donnell, 2008; Horan, Hajcak, Wynn, & Green, 2013; Kimhy et al., 2012; Livingston & Bracha, 1993; Tabak et al., 2015).

Social functioning deficits are also evident in individuals with premorbid disease status and in those who later develop schizophrenia (Davidson et al., 1999; Dworkin et al., 1993) and are often present in first-degree relatives of individuals with schizophrenia (Hans, Auerbach, Asarnow, Styr, & Marcus, 2000). Thus, social dysfunction is a candidate endophenotype for

schizophrenia that has important implications for the development, course, and outcome of this illness.

The most commonly studied aspects of social cognition in schizophrenia are emotion perception, social perception, theory of mind, and attributional style (De Herdt et al., 2013). Emotion perception (also called emotion recognition, affect recognition, or affect perception) is the ability to infer emotional information (i.e., what a person is feeling) from facial expressions, vocal inflections (i.e., prosody), or some combination of stimuli. Summarizing the broad literature in the field, the following key conclusions can be drawn (reviewed by Edwards, Jackson, & Pattison, 2002; Green et al., 2015; Kohler & Brennan, 2004; Mandal, Pandey, & Prasad, 1998). Individuals with schizophrenia display emotional processing/perception deficits compared to nonclinical controls and they present with more severe deficits in these domains compared to individuals with other psychiatric disorders such as depressive disorder (unless psychotic features are present). The greatest deficits are evident in the perception of negative emotions (compared with positive emotions). The deficit in emotion perception is stable over time, although evidence suggests that individuals in remission may outperform individuals in an acute phase of the disorder. Individuals with schizophrenia perform worse when trying to "read between the lines" (i.e., identifying what a given individual is thinking or feeling) but are less impaired on more concrete social judgments (i.e., identifying what a person is wearing or doing). For example, affective face perception has consistently been found to be impaired in patients with schizophrenia. Behaviorally, individuals with schizophrenia perform poorly when explicitly asked to identify facial expressions (Kohler, Walker, Martin, Healey, & Moberg, 2009). Many individuals with schizophrenia display restricted visual scanning and spend less time examining salient facial features during emotion perception tasks (Green & Phillips, 2004; Williams, Loughland, Gordon, & Davidson, 1999). Finally, impairments in emotion perception are present early in the course of illness (Addington, Penn, Woods, Addington, & Perkins,

2008; Kucharska-Pietura, David, Masiak, & Phillips, 2005). It needs to be noted that emotion perception and emotion experience are different abilities, and a large number of studies now indicate that, despite showing diminished emotional expressions, individuals with schizophrenia report normal levels of self-reported pleasure in response to stimuli in the laboratory and during their daily lives (Cohen & Minor, 2008; Kring & Elis, 2013; Green et al., 2015; Cohen & Minor, 2010). Research suggests that schizophrenia is associated with abnormal subjective experience of overwhelming emotions, personal distress and emotional contagion with negative emotions is stronger, but self-reports on emotion regulation and control of emotional expression are equivocal (Lehmann et al., 2014). Recent computational approaches into modelling anhedonia in patients (diminished capacity for pleasure) suggest abnormalities are specific to temporal dynamics of emotional expression, not general emotional expression (Strauss et al., 2020). Specifically, patients have deficits in the ability to sustain positive emotion over time and to maintain or increase these emotions (Strauss et al., 2020).

Social perception refers to a person's ability to ascertain social cues from behavior provided in a social context, which includes, but is not limited to, emotion cues (De Herdt et al., 2013). Social perception is also closely tied to social knowledge, which refers to a person's comprehension of social rules and conventions (e.g. as stored in social schemas); thus, these two abilities are interlinked. ToM involves both the ability to understand that others have mental states different from one's own and the capability to make correct inferences about the content of those mental states (e.g. others' intentions or beliefs; De Herdt et al., 2013). ToM is typically operationalized as participants' ability to understand false beliefs (first- or second-order ToM) or the ability to understand verbal hints. Impaired ToM or mentalizing in schizophrenia is well documented with meta-analyses indicating that patients have difficulty understanding the intentions of others from a cartoon panel and inferring the beliefs of others from simple written stories (Baron-Cohen, Wheelwright, Hill, Raste, & Plumb, 2001; Bora,

Yucel, & Pantelis, 2009b; Frith, 2014; Savla, Vella, Armstrong, Penn, & Twamley, 2012). The bulk of research supports the conclusion that this impairment in schizophrenia is a trait deficit. ToM deficits are present in both remission and non-remission samples, are not accounted for by deficits in general cognitive functioning and are not uniquely associated with any specific symptom type (e.g., paranoia; Savla et al., 2012). Finally, first-degree relatives of individuals with schizophrenia who also score high on schizotypy have impaired ToM (Irani et al., 2006) lending support for ToM as a potential endophenotype for schizophrenia.

Attributional style refers to an individual's characteristic tendencies in explaining the causes of events in their lives. Research indicates that individuals with persecutory delusions and/or paranoia tend to blame others, rather than situations, for negative outcomes, an attributional style known as a personalizing bias (Bentall, Corcoran, Howard, Blackwood, & Kinderman, 2001). Individuals with schizophrenia also show problems in monitoring the emotions of others, suggesting that they do exhibit impairments in empathic accuracy (Harvey, Philippe-Olivier, Zaki, Lee, Ochsner, & Green, 2012; Kern et al., 2013; Lee, Zaki, Harvey, Ochsner, & Green, 2011). These empathic accuracy deficits in schizophrenia are likely to begin with impaired perception of social information; that is, this impairment in schizophrenia seems to arise from a reduced ability to capitalize on the social cues being emitted by people that normally facilitate accurate interpretation of their moods (Lee et al., 2011). In summary, the social processes that are clearly impaired in schizophrenia (perception of social cues, mentalizing and emotion perception) are all considered reflective, meaning that they require effortful controlled processing (Green et al., 2015). By contrast, reflexive processes such as emotion experience, which require less mental effort than the other social processes, are relatively intact in this population (Green et al., 2015).

This, in turn, has directed researchers to examine whether social cognition can be improved in patients with schizophrenia (reviewed by Horan, Kern, Green, & Penn, 2008)

because enhancing this ability may be an important target for pharmacological and psychosocial treatments. Interestingly, there is little evidence that atypical medications improve social cognition in schizophrenia. Large adequately powered studies (Harvey, Patterson, Potter, Zhong, & Brecher, 2006; Kucharska-Pietura & Mortimer, 2013; Penn et al., 2009) have found that neither quetiapine nor risperidone (antipsychotic medications) resulted in improved emotion perception among 289 individuals with schizophrenia. Thus, there has been growing interest in psychosocial treatments and interventions as a means of improving social cognition.

Training programmes that target facial emotion perception and mentalizing deficits have been validated in individuals with schizophrenia (Kurtz & Richardson, 2011; Penn, Roberts, Combs, & Sterne, 2007). A meta-analysis of 19 studies consisting of 692 patients reported that these programmes show positive effects that are large in magnitude on some of the targeted social processes, namely facial affect recognition and ToM (Kurtz & Richardson, 2011). The analysis also revealed moderate to large effect sizes on improvement of total symptoms, community and institutional functioning showing the effects generalize to social functioning domains (Kurtz & Richardson, 2011). The evidence overwhelmingly indicates that social cognitive interventions are well tolerated, with high levels of subjective satisfaction and generally low levels of attrition across studies (Horan & Green, 2019). Furthermore, improvements in basic non-social neurocognition are not a prerequisite for improvements in social cognition. Two studies directly addressed this issue by comparing both social cognitive and neurocognitive outcomes in participants randomized to either social cognitive or cognitive remediation (Horan et al., 2011; Wölwer et al., 2005). Both studies found that social cognitive gains among these who received social cognitive treatment did not depend on neurocognitive changes. Further, those receiving cognitive remediation did not show significant improvements in social cognition.

Aside from improving performance on social cognition tasks, there is also preliminary evidence that social cognitive interventions can impact the neural systems that underlie social cognitive difficulties. Campos and colleagues (Campos et al., 2016) recently reviewed what they referred to as "neuroplastic effects" of social cognitive interventions. They summarized eleven studies that used a variety of neuroscientific approaches, including structural and functional MRI, electroencephalography (EEG), and magnetoecephalography (MEG). Despite relatively small sample sizes and highly diverse approaches to intervention, there was a wide range of neuroplastic training effects (e.g., reduced gray matter loss, increased regional brain activity, decreases in alpha range EEG activity) with effect sizes ranging from moderate to large (Campos et al., 2016). Of note, ten out of these 11 studies reported significant associations between behavioral improvement on social cognition tasks and neuroplastic changes (Campos et al., 2016).

1.3. Neurobiology of social cognition in schizophrenia

Social cognition relies on an extended neural system that comprises a wide range of highly intertwined, but specialized networks that allow for intact social behavior, emotion processing and responsiveness to affective stimuli (Brunet-Gouet & Decety, 2006; Burns, 2006; Burns, 2004; Fujiwara, Yassin, & Murai, 2015; Pinkham et al., 2003). There is clear evidence suggesting that the brain's visual areas such as the fusiform gyrus, the inferior occipital gyrus and the posterior superior temporal sulcus play a role in the early perceptual processing of facial stimuli (Fox, Iaria, & Barton, 2009; Fusar-Poli et al., 2009; Gobbini & Haxby, 2007). The temporoparietal junction extends from the superior temporal sulcus to the inferior parietal lobe and has been systematically associated with ToM tasks requiring participants to make inferences about others' intentions, and affective or cognitive states based on their behavior

(Saxe & Kanwisher, 2003; Saxe & Powell, 2006; Van Overwalle, 2009). Limbic areas also play a clear role in social cognition, specially contributing to facial emotion processing (Adolphs, 2009). Several limbic structures (anterior insula, cingulate and parahippocampal gyrus) have been linked to facial emotion recognition, but the most frequently studied structure has been the amygdala. The amygdala plays a critical role in classifying stimuli as salient as well as judging other people's faces (Adolphs, 2009), and as such is essential to understanding others' emotional states (Morris et al., 1998; Whalen et al., 1998). Schizophrenia is characterized by changes in the specific neuronal circuits connecting cortical and subcortical structures which integrate the social brain (Brunet-Gouet & Decety, 2006; Habel et al., 2010; Lee, Farrow, Spence, & Woodruff, 2004; Martin, Robinson, Dzafic, Reutens, & Mowry, 2014). Furthermore, many functional magnetic resonance imaging (fMRI) studies in schizophrenia patients have investigated the neural signatures of the social cognition impairments described in previous section.

Several studies have shown that individuals with and without schizophrenia have similar levels of neural activation in the fusiform area (Walther et al., 2009; Yoon, D'Esposito, & Carter, 2006) during non-affective face perception. However, the patterns of neural activation observed in patients were less cohesive (greater variability in engaging canonical activity patterns during classifications; Yoon et al., 2008), which could lead to poor performance on a relatively demanding non-affective face-perception task. Indeed, four meta-analyses of functional MRI studies and one meta-analysis of studies using event-related potentials (ERPs), mostly using face stimuli, demonstrate that there is aberrant neural activity associated with affective face perception in individuals with schizophrenia compared with healthy individuals (Anticevic et al., 2010; Delvecchio, Sugranyes, & Frangou, 2013; Li, Chan, McAlonan, & Gong, 2009; McCleery et al., 2015; Taylor et al., 2012). One meta-analysis focused on the amygdala and showed that individuals with schizophrenia showed decreased amygdala

activation compared with healthy controls when aversive emotional stimuli were contrasted with neutral stimuli, but not when aversive stimuli were presented alone (Anticevic et al., 2010). This finding suggests that the blunted response in the amygdala seen in individuals with schizophrenia during contrasts of emotional versus neutral conditions might be due to increased activation in response to neutral stimuli, a possible mechanism for abnormal salience attribution (Kapur, 2003). Another meta-analysis focused on facial affect tasks as measures of emotion processing and reported that, compared to healthy controls, patients with schizophrenia showed reduced activation throughout the entire facial affect processing network (parahippocampus, amygdala, thalamus, ventrolateral prefrontal cortex) and increased activation in visual processing regions, namely the cuneus (Delvecchio, Sugranyes, & Frangou, 2013). The function most consistently attributed to the cuneus relates to early stimulus categorization and modulating the quality or quantity of visual information reaching later processing stages (Sergent, Ohta, & MacDonald, 1992; Vanni, Tanskanen, Seppä, Uutela, & Hari, 2001). This pattern of reduced activation within visual cortex regions responsible for higher-order processing in schizophrenia was also observed by another meta-analysis of emotion processing (Taylor et al., 2012). Taken together, the findings strongly suggest that higher-order processing of complex visual stimuli (such as emotion) are impaired at multiple levels in patients. Functional MRI studies involving emotion perception and emotion experience tasks in schizophrenia also reported reduced amygdala activation for emotion perception specifically, but not for emotion experience (Taylor et al., 2012). Patients with schizophrenia are also characterized by reduced activation in medial cortical structures such as the hippocampus, and subcortical regions such as the striatum and thalamus during emotion processing (Taylor et al., 2012). The failure to activate medial temporal brain regions may lead to impairments judging the emotional significance of stimuli, a problem that is compounded when higher order cortical targets of the hippocampus and amygdala do not receive accurate

information to evaluate and respond to (Adolphs, 2009; Anderson & Phelps, 2001). Despite differences in the meta-analytic approaches used, these studies indicate that, for affective face perception, individuals with schizophrenia show less activation in the right inferior occipital gyrus, right fusiform gyrus, left amygdala and hippocampal regions, striatum, thalamus, anterior cingulate cortex, and medial prefrontal cortex (Delvecchio et al., 2013; Li et al., 2009; Taylor et al., 2012).

The brain regions identified as under activated in patients with schizophrenia during emotion perception (i.e. amygdala, hippocampus) work within a spatially and temporally defined circuitry to facilitate social functioning (Adolphs, 2003a; Critchley et al., 2000; Gorno-Tempini et al., 2001; Gur et al., 2002; Haxby, Hoffman, & Gobbini, 2002; Phan, Wager, Taylor, & Liberzon, 2002). This indicates that disruption at systems level, rather than discrete loci, may best explain the pattern of activation anomaly in schizophrenia. Several studies have considered functional connectivity in patients with schizophrenia during facial emotional perception. In a fear perception task, researchers found functional disconnection in autonomic and central systems in patients with paranoid schizophrenia (Williams et al., 2004). In the same fear detection task, others found that patients with schizophrenia had disconnections in a visual-amygdala-prefrontal system (Adolphs, 2004) and it has been suggested that basic visual-temporal dysfunction in schizophrenia may explain maladaptive appraisal of threat by patients (Leitman et al., 2008). Taken together, a possible lack of coordination in the orienting mechanisms, perceptual processing and prefrontal regulation of fear stimuli (Adolphs, 2004) indicates that patients' impairments could well be due to dysconnectivity across several brain regions (Das et al., 2007). Structural abnormalities in a neural circuit extending from limbic cortex through striatum, then thalamus, and finally reaching the prefrontal and cingulate cortex (Cheung et al., 2008; Ellison-Wright et al., 2008) are consistent with this concept of a network-wide interruption of social functioning in schizophrenia.

Neuroimaging studies have also shown a complex pattern of aberrant neural activation in individuals with schizophrenia during mentalizing in various tasks. Several studies found that patients had decreased activity in core regions of the mentalizing system. For instance, when inferring emotions from pictures of eyes, patients showed reduced activation of the left inferior frontal gyrus compared with controls (Russell et al., 2000). During a task that required participants to use the perspectives of others to correctly identify objects, patients showed reduced activation of the ventromedial prefrontal cortex and orbitofrontal cortex (Eack, Wojtalik, Newhill, Keshavan, & Phillips, 2013). Patients also showed decreased activation of the medial prefrontal cortex and temporoparietal junction while making inferences about the beliefs of others (Brüne, 2005; Dodell-Feder, Tully, Lincoln, & Hooker, 2014; Lee, Junghee, Quintana, Nori, & Green, 2011). Furthermore, controls showed less activation in the mentalizing system when inferring the intentions of a person in isolation compared with inferring the intentions of a person who is participating in a social interaction, and patients failed to show this modulation (Walter et al., 2009). Patients also showed reduced activation of the bilateral temporoparietal junction and inferior frontal gyrus while viewing interacting geometric shapes (Das, Lagopoulos, Coulston, Henderson, & Malhi, 2012).

However, some studies have reported that individuals with schizophrenia exhibit hyperactivation or delayed activation of certain brain regions during mentalizing tasks. For instance, patients showed increased activity in the superior temporal gyrus and medial prefrontal cortex when tasked with inferring emotions from pictures of eyes, compared with healthy controls (de Achával et al., 2012). Another study found that, compared with controls, people with schizophrenia exhibited increased activity in the superior temporal gyrus, dorsomedial prefrontal cortex and precuneus when inferring the intentions of others (Brüne et al., 2008). In both of these studies, the individuals with schizophrenia showed intact performance, suggesting that they required greater levels of neural activity to achieve the same

levels of performance on mentalizing tasks as healthy controls. In addition, these findings of increased neural activity in mentalizing regions fit with the tendency of some individuals with schizophrenia to over-attribute intention to others. This tendency, called hypermentalizing, has been linked to paranoid symptoms of schizophrenia (Ciaramidaro et al., 2014; Frith, 2004). Finally, a study using animated geometric shapes found that patients showed decreased activation in the temporoparietal junction during the first half of the task, compared with controls, but increased activation in the same brain region during the second half of the task (Pedersen et al., 2012). This finding may suggest that individuals with schizophrenia infer the mental states of others more slowly than healthy individuals, rather than that they have an overall impairment in mentalizing ability.

Functional MRI findings also mirror behavioral results of normal emotion experience in patients with schizophrenia (Cohen & Minor, 2008; Kring & Elis, 2013). For example, individuals with schizophrenia consistently show normal striatal responses to monetary rewards, and a recent meta-analysis found no differences between patients and controls in activation in brain regions typically associated with emotion experience (Kring & Elis, 2013; Taylor et al., 2012). Individuals with schizophrenia report normal levels of negative emotion to unpleasant stimuli, but they also report elevated levels of negative emotion in response to neutral and pleasant stimuli, compared with healthy controls (Kring & Elis, 2013; Taylor et al., 2012). Similarly, in fMRI studies, patients show normal activation of the amygdala and other relevant regions during exposure to unpleasant stimuli (Kring & Elis, 2013; Taylor et al., 2012). Although some studies find amygdala hypoactivity during contrasts of unpleasant versus neutral stimuli, this pattern may reflect amygdala hyperactivity to neutral conditions in patients rather than hypoactivity to negative stimuli (Hall et al., 2008; Holt et al., 2006) and they showed ventrolateral prefrontal cortex hypoactivation while emotional responses were decreased and ventrolateral prefrontal cortex hyperactivation while emotional responses were increased.

Furthermore, neural activity in the amygdala was inversely coupled with prefrontal cortex activation in controls, but not in those with schizophrenia (Morris, Sparks, Mitchell, Weickert, & Green, 2012).

In summary, the broad neuroimaging literature investigating social cognition deficits concludes that schizophrenia is associated with wide ranging impairments (Brunet-Gouet & Decety, 2006; Habel et al., 2010; Lee et al., 2004; Martin, Robinson, Dzafic, Reutens, & Mowry, 2014). The next chapter of this thesis will present a systematic review outlining the neural correlates of social cognition in populations at risk for psychosis, such as CHR and schizotypy samples. Thus, the next chapter will summarize existing knowledge and serve as a basis for outlining gaps in the literature.

Chapter Two

Neural correlates of social cognition in populations at risk of psychosis: A systematic review

Abstract

Social cognition refers to the mental operations governing social interactions. Recent research has highlighted the importance of social cognition in determining functional outcome in patients with schizophrenia and in psychosis risk populations. The aim of this review is to investigate the neural correlates of social cognition in different psychosis risk populations, potentially representing different levels of risk i.e. high schizotypy (SR), familial risk (FR) and clinical high risk (CHR). PsychINFO, Web of Science and PubMed were systematically searched, and 39 papers were included in the final review. Results in FR samples were highly inconclusive. In SR samples, findings showed a tendency towards increased task related activity in frontal cortex regions. The most consistent results come from CHR samples, where findings suggest increased task related activity in frontal and cingulate cortices. Interestingly, all studies of CHR populations also report increased activity in temporal cortex and abnormal response to neutral stimuli during emotional processing tasks. These findings are discussed in relation to dopamine models of psychosis due to temporal cortex abnormality.

List of abbreviations used for neural regions:

ACC – anterior cingulate cortex

dlPFC – dorsolateral prefrontal cortex

dmPFC – dorsomedial prefrontal cortex

IFG – inferior frontal gyrus

mPFC – medial prefrontal cortex

OFC – orbitofrontal cortex

PCC – posterior cingulate cortex

PFC – prefrontal cortex

SFG – superior frontal gyrus

STG – superior temporal gyrus

STS – superior temporal sulcus

TPJ - temporal-parietal junction

vlPFC – ventrolateral prefrontal cortex

vmPFC – ventromedial prefrontal cortex

2.1. Introduction

Schizophrenia is a severe mental health disorder encompassing a heterogeneous cluster of symptoms such as delusions, hallucinations, cognitive impairment, lack of motivation and observable social cognition biases (among other; Frith, 2014). This debilitating psychiatric

condition affects nearly 1% of the general population, thus early clinical intervention has become a major objective of mental health services and research networks (McGorry, Killackey, & Yung, 2008). Crucially, treatment advances have been hampered, because whilst antipsychotic medication has been shown to be efficacious for treating positive symptoms (delusions, hallucinations), these drugs are largely ineffective for the treatment of social cognition deficits that are also prevalent in the disorder (Haddad, Brain, & Scott, 2014). As such, focused research into the pathological neural mechanisms that underlie social cognition deficits is needed to facilitate targeted interventions. This is important because poor social functioning has been linked to a reduced quality of life (Penn, Corrigan, Bentall, Racenstein, & Newman, 1997) and predicts illness outcome in schizophrenia, including relapse, poor illness course and unemployment (Couture, Penn, & Roberts, 2006).

Social cognition refers to the mental operations involved in understanding other people's thoughts and intentions, recognising and perceiving emotions and understanding social interactions (Brothers, 1990; Adolphs, 2001). Although social and non-social cognition share some overlapping operations (e.g. working memory, perception, etc.), some brain regions and networks have specifically been linked to processing social information (Green, Horan, & Lee, 2015). Neural systems involved in processing social-affective stimuli, such as facial emotion and nonverbal social cues, include the amygdala, ventral striatum, ventromedial prefrontal cortex, anterior cingulate cortex and superior temporal regions (Ochsner, 2008; Adolphs, 2009; Fig 1). Higher level social cognition processes, such as inferring the intentions of others, are most commonly associated with activations in a broad 'mentalizing network' including the medial frontal cortex, paracingulate and posterior cingulate cortex, temporal-parietal junction, superior temporal sulcus, and the temporal pole (Ochsner, 2008; Adolphs, 2009; Fig 2).

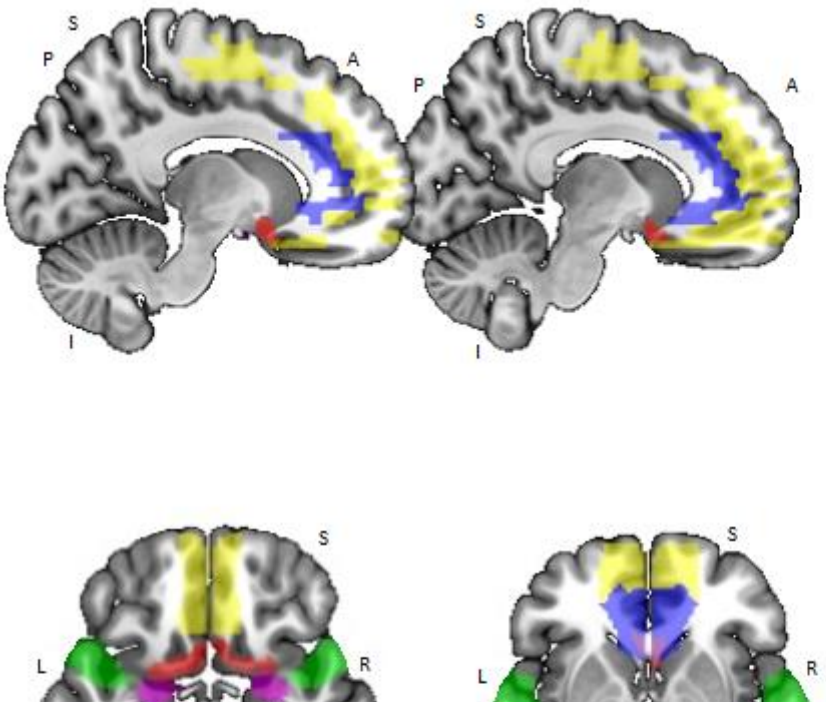

Figure 1. **Areas involved in the recognition and respone to social-affective stimuli**. The amygdala (purple) is responsible for recognising emotional expressions and evaluating stimuli. The ventral striatum (red) is associated with recognising stimuli with learned reward values. The medial prefrontal cortex (yellow) supports the ventral stiatum, a10nd is further involved with interpreting nonverbal social information and the contextual interpretation of complex social information. The anterior cingulate cortex (blue) is associated with like/dislike judgements of social cues and intergrating this with emotional information to motivate behavior. The superior temporal gyrus (green) is imporant for recognising nonverbal social cues.

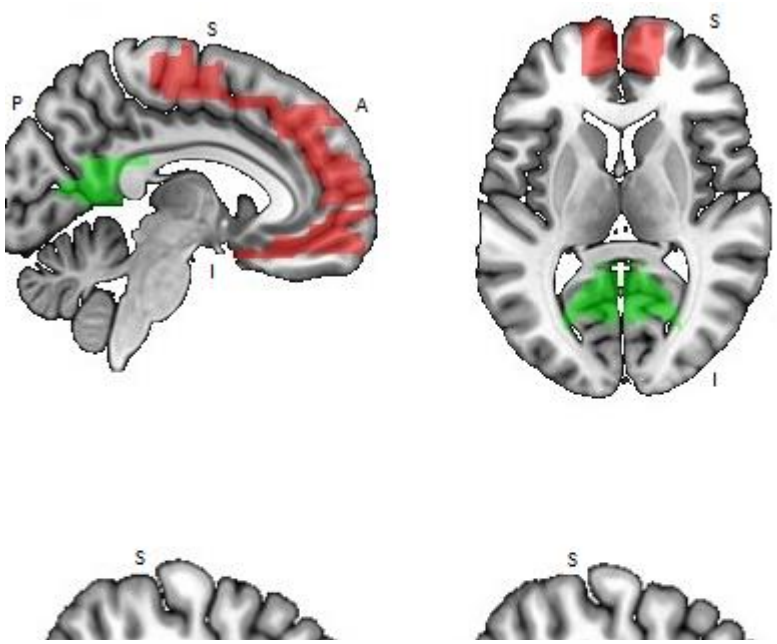

Figure 2. **Areas involved in higher-level mental inference.** The medial prefrontal cortex (red) is the most reliably activated structure across these studies. This region is associated with thinking the internal states of others, inferring the current beliefs of others and evaluating their long-term traits. The posterior cingulate cortex (green) is associated with generating knowledge of our mind and those of others. The temporal-parietal junction region (purple) is associated with imaging the perspectives of others and attributing beliefs and internal states to others. The superior temporal sulcus (blue) and the temporal poles around it are associated with representing nonverbal cues (that are relevant to deciphering the intentions of others) and with representing emotional knowledge.

Patients with schizophrenia show widespread impairment in the processing of social information, particularly when processing emotional stimuli and when inferring the intentions of others (Green, Horan, & Lee, 2015; Ventura, Wood, Jomenez, & Hellemann, 2013). These social cognitive deficits can result in misinterpretations of the social intent of others, leading to social withdrawal, impaired day-to-day social functioning (Fett, Viechtbauer, Penn, van Os, & Krabbendam, 2011) and delusional interpretations (Morrison, Renton, Dunn, Williams, & Bentall, 2004). At a neural level, functional Magnetic Resonance Imagining (fMRI) studies in

schizophrenia patients have shown reduced activation (relative to healthy controls) in a number of brain regions during social cognition tasks, namely the medial prefrontal cortex (mPFC), the anterior insula and the amygdala (Anticevic & Corlett, 2012; Whalley, et al., 2009; Taylor, Liberzon, Decker, & Koeppe, 2002; Takahashi et al., 2004). Patients with a first-episode psychosis also present with abnormal corticolimbic response to emotional stimuli (Bergé et al., 2014), with altered neural activity to emotional relative to neutral scenes (Modinos et al., 2015). These abnormalities are seen in patients with schizophrenia during Theory of Mind (ToM; inferring the intentions of others) tasks, with reduced activity observed in middle/inferior frontal gyrus and insula (Russell et al., 2000), the mPFC (Lee et al., 2006; Brunet, Sarfati, Hardy-Bayle, & Decety, 2003) and the TPJ (Brüne et al., 2008). Conversely however, there are studies that report increased activity relative to healthy controls in mPFC, superior temporal sulcus/gyrus (STG) and TPJ during ToM tasks (Shamay-Tsoory et al., 2007; Pedersen et al., 2012).

These broadly consistent fMRI findings demonstrating functional abnormalities during social cognition tasks have provided support for the notion that these deficits are a strong candidate endophenotype for schizophrenia (Green, Horan & Lee, 2015). Indeed, social cognition impairments have been found to be longitudinally stable and present during both acute symptom stages of the illness and during clinical remission. Research is also increasingly identifying abnormal neural processing in social cognition tasks in psychosis-risk populations (Braff, Freedman, Schork, & Gottesman, 2006), suggesting the presence of this impairment during the illness prodrome and in other high-risk states. Moreover, social cognition deficits can predict functional outcomes in patients with schizophrenia (Kring & Elis, 2013; Brüne, Schaub, Juckel, & Langdon, 2011; Alvarez-Jimenez et al., 2012) and are one of the most predictive traits for future onset of schizophrenia-spectrum disorders in psychosis risk populations (Kwapil, 1998). Thus, specifying the nature and extent of these social cognition

deficits, and the corresponding neural abnormalities, in different psychosis risk populations may help built a comprehensive model of the progression of this potential endophenotype during illness prodrome.

The aim of this systematic review is to identify patterns of neural abnormalities associated with social cognition across different psychosis risk populations. Firstly, schizotypal personality traits are believed to represent an underlying vulnerability for psychosis (Raine, 1991; Meehl, 1990, Nelson, Seal, Pantelis, & Phillips, 2013; Ettinger, Meyhöfer, Steffens, Wagner, & Koutsouleris, 2014). Furthermore, research has consistently demonstrated similarities between schizotypy and schizophrenia with parallel, albeit attenuated symptoms and deficits (Nelson, Seal, Pantelis, & Phillips, 2013; Ettinger et al., 2014). While the majority of healthy individuals with high schizotypal traits (schizotypy risk, SR) do not develop psychosis, the rate of SR participants meeting criteria for a schizophrenia-spectrum diagnosis at a 10-year follow-up assessment is estimated to be around 2% (Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Kwapil, Gross, Silvia, & Barrantes-Vidal, 2013; see van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009 for a review).

Thus, research into SR populations may represent a useful paradigm for investigating etiological factors associated with schizophrenia in individuals not presenting with typical confounding factors present in clinical samples (i.e. comorbidities, medication).

Insights into at-risk populations also originate from genetic studies. Previous findings from family, twin and adoption studies conclude that familial factors are important risk predictors for the development of psychosis (familial risk – FR; Fowles, 1992). First-degree nonpsychotic relatives of schizophrenia patients have a 10% risk of developing psychosis (MacDonald & Schulz, 2009). In addition, a link between genetic vulnerability to psychosis

and the expression of subclinical psychotic-like experiences has been demonstrated (Fanous, Gardner, Walsh, & Kendler, 2001).

Finally, the research potential of clinical high-risk (CHR) groups has been increasingly recognised. This risk category is used to identify individuals potentially in a prodromal phase of psychosis and is operationally defined by attenuated psychotic symptoms and a decline in social and occupational function (Fusar-Poli et al., 2013; Yung et al., 1998; Yung et al., 2003). CHR individuals have an elevated risk (relative to the general population) of developing a first episode psychosis with transition rates varying form 18% after 6 months of follow-up to 36% after 3 years (Fusar-Poli et al., 2012).

We have chosen to focus on these three psychosis risk categories as they outline different risk levels in terms of subsequent development of psychosis and might provide valuable insights into disorder progression and neurofunctional risk trajectories. For each at-risk group, we provide a summary of the key neural findings based on brain region in the frontal cortex, cingulate cortex, limbic and subcortical regions (medial temporal regions, insula cortex, striatum and thalamus) and the lateral temporal cortex across a variety of social cognition tasks (i.e. emotional processing, ToM tasks, social reward tasks).

2.2. Methods

The systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher, Liberati, Tetzlaff, & Altman, 2009) guideline. The review is registered with Prospero under registration number CRD42018111771.

2.2.1. Inclusion criteria

The aim was to identify all studies fulfilling the following criteria: fMRI studies investigating social cognition in at-risk for psychosis populations (SR, FR, CHR). Social cognition, as outlined in the Introduction, refers to a diverse range of mental operations underlying social interactions (Adolphs, 2001). Thus, tasks were defined as engaging social cognition mechanisms if they: involved perceiving the intentions/dispositions of others, perceiving/recognising emotions or otherwise involved processing demands that are elicited by, about, and/or directed towards other people. To be included, studies had to provide enough methodological details to judge the social cognition nature of the tasks (have specific a-priori hypotheses as to how the tasks will activate areas within the social brain network, etc.).

There was no age limit applied to the samples although many CHR samples include individuals between 18 – 35 years of age (Fusar-Poli et al., 2012; Fusar-Poli et al., 2013). At-risk populations included samples of healthy participants in the general population scoring high on schizotypy personality traits (SR), participants at familial risk of developing psychosis (FR), and at-risk/high clinical risk populations (CHR; Yung et al., 1998). Samples consisting of individuals presenting with schizophrenia-like symptoms that do not yet warrant full diagnosis were included in categories depending on the nature of the assessment measure used. Studies had to index at-risk populations via a validated measure (e.g. Schizotypy Personality Questionnaire, Comphrenesive Assessment of at-risk mental states, Structured Clinical Interviews for DSM-V, etc.) or had to clearly define genetic risk (i.e. first-degree relatives of patients with schizophrenia). Studies that utilised social anhedonia measures as representing psychosis risk were included in the SR review, as per previous findings indicating that social anhedonia identifies individuals with current elevated positive and negative schizotypy traits

and is an indicator of schizotypy (Blanchard, Gangestad, Brown, & Horan, 2000; Blanchard, Collins, Aghevli, Leung, & Cohen, 2011).

To qualify for inclusion, studies had to present original work subjected to peer-review. PhD theses matching the aim of the review were included if they were published. Studies that did not report fMRI results in the risk group of interest relative to healthy controls were excluded.

2.2.2. Search strategy and selection of studies

Articles published up to November 2018 were identified through literature searches conducted on PsychINFO, Web of Science and PubMed using search terms following Boolean logic. The initial search on all databases used: ''social cognition'' AND (''neuroimaging'' OR ''functional imaging'') AND schizo*. Secondary searchers to ensure optimal identification used: ''social cognition'' AND (''neuroimaging'' OR ''functional imaging '') AND schizo* AND (''clinical high risk'' OR ''ultra-high risk'' OR ''at risk mental state'' OR ''prodromal psychosis''). References from articles and secondary searches and relevant literature reviews were also examined for possible inclusion in the review.

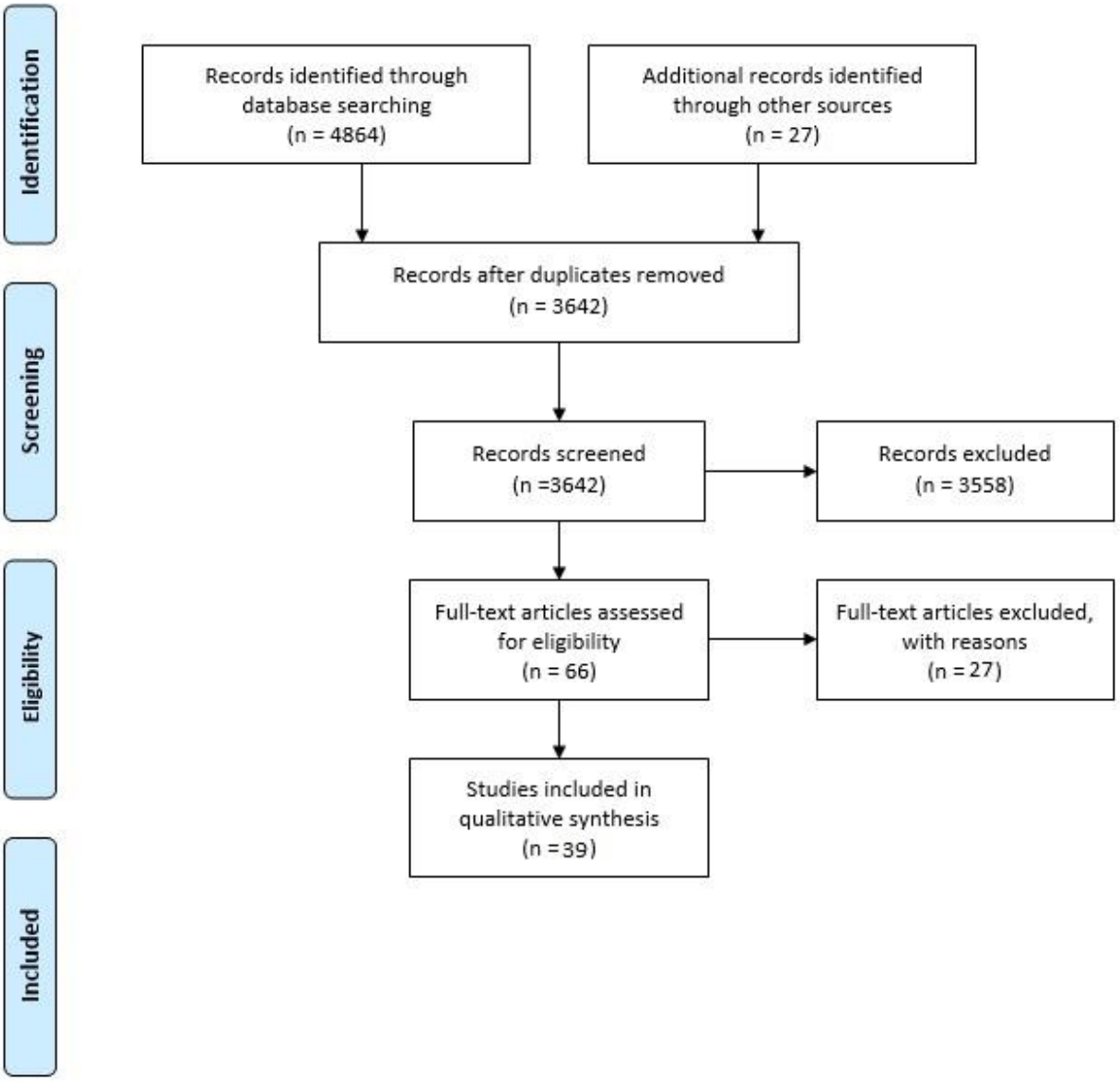

Figure 3. PRISMA flowchart of the systematic review process.

Database hits, exclusion, secondary searches and final inclusion were summarised in a PRISMA diagram (Fig 3). We found 4864 records from initial searches. After adjusting for duplicates, 3597 articles were screened for title and abstract. Out of these, 3558 records were discarded as the studies did not meet the inclusion criteria. The full texts of the remaining 39 articles were assessed for eligibility and 21 of these papers were included in the review.

Additionally, the reference lists of these articles were searches for relevant records, this search yielded 27 additional articles. Of these secondary searchers, 18 articles were included in the review. Thus, out of 66 full-text screened papers, the total number of articles that met criteria for inclusion was 39.

A second reviewer (FS) independently screened title and abstract of 15% of the 3597 articles identified from the initial search (541 articles). Subsequently, the same author independently screened 15% (6 articles) of the 66 papers identified for full-text screening (from both database and secondary searches). Disagreements, if present, were solved via research team decision. Two authors (PK, FS) further assessed the full list of 39 final included articles to ensure they meet inclusion/exclusion criteria.

2.2.3. Data collection

The following information was extracted from each included study: (1) authors and year of publication, (2) sample size, (3) type of measure used to define psychosis risk, (4) methodologies and task specifics, (5) fMRI findings in risk group relative to healthy control and (6) main conclusions.

2.2.4. Quality assessment

To ascertain quality individual studies were appraised using the STROBE checklist (Von Elm, et al., 2007). This is a structured, standardised checklist consisting of 22 items, each relating to the different sections in an article (i.e. title, abstract, introduction, methods, results, discussion, and funding). The quality scores calculated for each article (total score 22) give

comparisons of the relative quality of included studies, a higher score indicating higher quality (Table S1 includes the quality scores for all studies).

2.3. Results

2.3.1. Samples, demographics, and study design

The search identified 13 fMRI studies investigating social cognition in SR samples, 16 studies in FR and 10 studies CHR samples. Studies used a variety of established methods to assess risk populations (see Table 1, 2 and 3 for relevant populations).

Samples, demographics, key findings and task details are outlined in Table 1 (SR), Table 2 (FR) and Table 3 (CHR). Sample sizes ranged from 10 to 260 participants (mean sample size 67, standard deviation 97). Total number of SR subjects in this review was 287 (relative to 287 controls), total number of FR was 406 (relative to 613 controls) and total number of CHR subjects was 594 (relative to 525 controls). All studies utilised a cross-sectional design, with no randomised control trials included in the review. Emotional processing tasks were used in 24 studies, ToM tasks were used in 9 studies, and 6 papers outlined different tasks reported to engage social cognition. All studies included in the review reported results relative to healthy controls (or groups low on schizotypy symptomatology for SR studies), and the all results presented here report differences relative to control groups. Subjects in the SR and FR groups were not medicated, a subset of the CHR subjects were medicated at the time of scanning (the studies that included medication status as confound did not report significant differences, please see supplementary table 2). Due to the small number of medicated subjects (only in CHR groups), we could not assess the effect of medication on the results.

We further conducted analyses based on age and functional task design to rule out systematic differences between the at-risk groups and the controls based on these factors. Lower level social cognition tasks (i.e. emotion processing, emotion viewing tasks, etc.) were used in 10 studies with SR samples, 8 studies with FR samples and 7 studies with CHR samples. Higher level social cognition tasks (e.g. ToM) were used in 3 SR studies, 8 FR studies and 3 CHR studies. The functional task design was not significantly different between risk groups and controls, $x2\ (2) = 2.46$, $p > .05$. No interactions were found between risk groups and controls in terms of age either, $x2\ (2) = .01$, $p > .05$. Finally, the three at-risk populations did not differ significantly on age, $F\ (1,71) = .37$, $p > .05$. Details on age, level of education and type of task are in supplementary table 1. Quality scores for the included studies ranged from 16 to 21. The mean quality score for the SR studies was 17.96, for the FR group was 18.37, for the CHR group was 21.7 (details in supplementary table 1).

The results of this review were categorised in four separate brain networks, namely frontal cortex, cingulate cortex, limbic regions and the lateral-temporal cortex. This organisation broadly represents the separate brain regions and networks involved in social cognition as outlined in the literature (Adolphs, 2009) and serves as a comprehensive framework to use for tabulating results.

Table 1. Summary of included papers investigating SR samples.
Blue shading – decreased activity. Grey shading – increased activity. Orange shading – mixed results.

Study ***(year)***	***Sample size*** ***(healthy controls)*** ***Measure***	***Task***	***Frontal cortex*** *(Risk group vs controls)*	***Cingulate cortex*** *(Risk group vs controls)*	***Limbic regions*** *(Risk group vs controls)*	***Lateral temporal cortex*** *(Risk group vs controls)*	***Conclusions***
Wang et al., 2018	*34 (30 low schizotypy)* *Chapman Psychosis Proneness Scales*	*Facial Emotional Valence Discrimination Task. Emotions: angry, fearful, happy, neutral.*	*↓ mPFC (neutral condition) ** ↑ middle frontal gyrus****	*↑ ACC (angry conditions) ****	*↓ amygdala (fearful and neutral conditions) ** ↑ insula (angry conditions) ****		*Abnormal emotional processing neural correlates.* *Altered activity in the prefrontal regions may result in the dysregulation of negative emotions, or it might be related to possible compensatory mechanisms.* *Hyperactivation of the insula observed in the present study may suggest that there may be a stronger negative emotional response to angry faces in social interaction.*

Modinos et al., 2017	*23 (25 low schizotypy)* *O-LIFE*	*Emotional processing task. Categories: negative high arousal, negative low arousal, positive high arousal, positive low arousal, neutral matched for social content.*	*↑ mPFC***	*↑ ACC***	*↑ hippocampus***		*Dysfunction of the circuitry underlying emotional processing.*
Modinos, Ormel, & Aleman, 2010	*17 (17 low schizotypy)* *CAPE*	*Passive viewing emotional task. Conditions: negative, reappraise, neutral.*	*↑ left dmPFC*** *↑ right vlPFC***	*↑ ACC***			*Dysfunction of the circuitry underlying emotional processing.* *Greater activation of prefrontal cognitive control regions is required to down-regulate the experience of negative emotions.*

Huang et al., 2013	*14 (14)* *SPQ*	*Dynamic facial expression processing. Emotion – happy. Conditions: Happiness induction interaction cues (praise); happiness reduction interaction cue (blame).*		*↓ left PCC (blame conditions) *** *↓ rACC (happiness disappearing conditions) ***		*↓ right STG* *(blame conditions) ***	*Less deactivation in the ACC in the happiness disappearing condition might suggest alteration of neural activities in the hedonic system of individuals with SPD traits.* *The more deactivated STG in the 'blame' condition could provide a piece of evidence of neural sensitivity for the negative social interaction cues, which induced unhappiness in individuals with SPD traits.*
Modinos, Renken, Ormel, & Aleman, 2011	*18 (18)* *CAPE*	*Self-reflection task (self vs other vs general semantic processing)*	*↑ right dmPFC*** *↑ left vmPFC*	*↓ PCC (self vs other contrasts) ***	*↑ bilateral insula* *(negative self vs semantic) ***		*High PP subjects may make less favourable judgements about the other person.*

			*(positive self vs semantic) *** *↑ right dmPFC* *(negative self vs semantic) ***	*↑ ACC (negative self vs semantic conditions) ***			*High PP subjects may be characterised with exertion of higher cognitive control to diminish emotional response.* *High PP subjects may have an increased emotional response to self-related stimuli of positive and negative valence (vmPFC), which is seemingly associated with attempts to diminish this response (activity in dmPFC).*
Premkumar et al., 2012	*12 (14)* *O-LIFE (UE subscale)*	*Rejection-acceptance task (images depicting social acceptance, social rejection or neutral scenes).*	*↓ left vmPFC/vlPFC* *(rejection vs neutral) ***	*↓ dACC bilaterally (rejection vs neutral conditions) ***			*HS subjects may be unable to attend to and process rejection cues.* *HS subjects may be unable to attend to and process rejection cues and may not be*

							able to effectively engage prefrontal regions in conflict detection and emotional decision-making.
Wang et al., 2015	*52 (-)* *Chapman Psychosis Pronesess scales*	*Theory of Mind task. One or two characters in them.*	***Positive correlation** between negative schizotypy and activity in medial frontal gyrus** ***Negative correlation** between positive symptoms and activity in the medial frontal gyrus*			***Positive correlation** between bilateral middle temporal gyrus activity and negative schizotypy** ***Positive correlation** between right TPJ activity and negative schizotypy**	*Negative schizotypy associated with poorer social cognition and compensatory mechanisms.* *Negative schizotypy is associated with poorer social cognition.*
Germine, 2012	*15 (15)* *Revised Chapman Social Anhedonia Scales*	*Emotional faces task - emotion discriminations vs identity discriminations vs pattern discriminations.*	*↓ anterior portion of the rostral PFC***			*↓ right STG*** *↑ left fusiform gyrus***	*Deactivation of areas during emotion processing.* *Social anhedonia is related to differences in the neural subtracted responsible for*

							self/other representations.
Modinos , Renken, Shamay-Tsoory, Ormel, & Aleman, 2010	*18 (18 low)* *CAPE ¶*	*First and second order Theory of Mind Mental state attributions.*	*↑ anterior mPFC*** *↑ lateral PFC bilaterally*** *↑ right dmPFC (during second order ToM) ***				*Require greater effort to integrate separate cognitive operations to correctly mentalize and reach performance equivalent to controls.*
Healey, Morgan, Musselman, Olino, & Forbes, 2014	*27 (-)* *Revised Chapman Social Anhedonia Scale*	*Social Rewards Task – passive viewing task. Face stimuli: either people who gave them positive social feedback or ambiguous social feedback.*	***Positive correlation*** *between mPFC activity and anhedonia scores***				*Anhedonia is associated with disrupted neural responding to peer social feedback.* *Anhedonia might be associated with an abnormal response to mutual liking as if it were aversive or, alternatively, received linking as if it were less salient.*

Mohanty et al., 2005	*17 (17)* *Chapman Psychosis Pronesess scale*	*Emotional Stroop Task (positive, negative, neutral words).*	*↑ right middle frontal gyrus*** *↑ IFG* *(negative stimuli) ***		*↑ amygdala cluster*** *↓ nucleus accumbens***		*Exaggerated attention to negative stimuli even though they are task irrelevant.* *Increased IFG activity may indicate a greater effort to inhibit strongly interfering emotional stimuli to achieve normal behavioural performance.* *Decreased activity in the nucleus accumbens suggests mechanisms for dysregulation of inputs form important brain regions in the face of aversive stimuli.*
Premkumar et al., 2013	*12 (12)* *O-LIFE (UE subscale)*	*Criticism listening task (relative's criticism, positive or neutral comments).*	*↓ right middle frontal gyrus* *(positive vs neutral) ***		*↓ left insula*** *↓ right thalamus*	*↓ left STG* *(positive vs neutral) ***	*HS subjects may be characterised by reduced capacity to elevate mood in response to reward and by difficulty in*

					*(positive vs neutral contrasts) ** *		*positive emotion regulation.*
Chan et al., 2016	*28 (-)* *Chapman Social Anhedonia scale†*	*Affective Delay Task (emotional stimuli as reward or loss based on RT to the target).*			*↓ left thalamus* *↓ right insula* *(positive vs neutral) **		*Affective incentives may elicit specific activations in high anhedonia subjects.*

† low vs high N is not reported for the low-high anhedonia comparison.

¶ same sample as Modinos et al (2011)

* significant at p<0.005 or p<0.001 uncorrected

** significant at p < 0.05 corrected

Table 2. Summary of included papers investigating FR samples.
Blue shading – decreased activity. Grey shading – increased activity. Orange shading – mixed results.

Study ***(year)***	***Sample size*** ***(healthy controls)*** ***Measure***	***Task***	***Frontal cortex*** *(Risk group vs controls)*	***Cingulate cortex*** *(Risk group vs controls)*	***Limbic regions*** *(Risk group vs controls)*	***Lateral temporal cortex*** *(Risk group vs controls)*	***Conclusions***
Villarreal et al., 2014	*14 (14)* *Siblings, no SCID-I diagnoses*	*Basic emotion task, Faces Theory of Mind Task, Eyes Theory of Mind Task* *Correlated measures – Social Skills Performance Assessment questionnaire; Test for Adaptive Behaviour in Schizophrenia*	***Positive correlation*** *between bilateral dlPFC, bilateral IFG activation and SSPA during basic emotion processing** ***Positive correlation*** *between bilateral SFG, left middle frontal gyrus activation and SSPA during ToM tasks**	***Positive correlation*** *between left cingulate gyrus and SSPA during ToM**	***Positive correlation*** *between insula and SSPA during basic emotion processing**		*Faulty/alternative brain processing underlying social competence.*
Spilka & Goghari, 2017	*27 (27)* *Siblings, no SCID diagnoses*	*Theory of Mind task. Judge changes in the character's affective state – better, worse, equal compared to preceding picture.*	*No differences found*	*↑ PCC***			*Posterior ToM regions might be inefficiently hyperactivated.* *May represent a compensatory mechanism that*

							maintains intact performance.
van Buuren, Vink, Rapcencu, & Kahn, 2011	*24 (25)* *Siblings, no MINI or SCAN diagnoses*	*Emotional valence rating task. Conditions: negative, positive, neutral.*	*↑ vmPFC*** *↑ dmPFC*** *↑ right middle frontal gyrus (emotional relative to neutral stimuli) ***	*↑ PCC*** *↑ ACC*** *(emotional relative to neutral)*	*↑ bilateral amygdala*** *↑ hippocampus* *(emotional relative to neutral) ***	*↑ middle temporal gyrus***	*Hyperactivity supports the notion of abnormal social cognitive processing in FR subjects.* *Abnormal social cognitive processing.* *Hyperactivity supports the notion of abnormal social cognitive processing in FR subjects.* *Abnormalities in the neural circuitry of emotion processing.*
Pulkkinen et al., 2015	*51 (52)* *Siblings, no SCID/SIPS diagnoses*	*Visual presentation of dynamic happy or fearful faces.*	*↑ SFG***	*↓ anterior paracingulate cortex* *(happy conditions) ***			*May not have the same vivid response to dynamic happy faces, which may be a risk factor for social withdrawal due to a*

							lack of enjoyment of social interactions. *Trait of increased effort for emotion recognition.* *Reduced functional connectivity may lead to functional compensations in other brain regions as they take a greater role in processing emotions.*
Walter et al., 2011	*42 (18)* *Risk allele carriers (rs1244706)*	*ToM task*	*↓ dmPFC*** *↓ left lateral PFC***	*↓ PCC***			*Impaired neural ToM correlates in RA carriers.* *Reduced top down influence of the DLPFC on the posterior TOM system, possibly compensated by increased connectivity between the posterior parts of*

							the TOM system and the inferior PFC as part of the mirror neuron system.
de Achával et al., 2013	*13 (13)* *Siblings, no SCID-I diagnoses*	*Modified moral dilemmas task. Subject had to judge the character's action based on a dilemma.*	*↑SFG*** *↑IFG***				*May represent a compensatory mechanism.*
de Achával et al., 2012	*14 (14)* *Siblings, no SCID-I diagnoses*	*Basic emotion task, Faces Theory of Mind Task, Eyes Theory of Mind Task.*	*↓ right prefrontal structures during emotion processing**		*↑ bilateral insula**		*Failure to recruit right brain structures during emotion processing tasks.* *May be due to a failure to recruit right brain structures during emotion processing tasks.*
Spilka, Arnold, & Goghari, 2015	*27 (27)* *Siblings, no SCID-1 diagnoses*	*Passive viewing facial emotion perception task. Emotions – happy,*	*↑ left IFG (fearful vs neutral) ***		*↑ left insula* *(fearful vs neutral contrasts) ***	*↓ fusiform gyrus***	*May reflect compensatory mechanisms.*

		sad, neutral, fearful, angry).	*↑ left OFC (fearful vs neutral) ***			*↑ left temporal pole (fearful vs neutral contrast) ***	*Characterised by under-recruitment of regions involved in processing perceptual features of faces.* *Under-recruitment of regions involved in processing perceptual features of faces.*
van der Meer et al., 2014	*20 (20)* *Siblings, no SCAN or Mini-Plus diagnoses*	*Emotion regulation Task. Conditions: attend neutral, attend negative, and reappraise, supress.*	*↓ left vmPFC**		*↓ amygdala**	*↓ STG**	*Hypoactivation may be related to compromised cognitive control and emotion regulation.*
Mohnke et al., 2015	*63 (297)* *Siblings, no SCID diagnoses*	*Theory of Mind task. Judge changes in the character's affective state – better, worse, equal compared to preceding picture.*	*↓ mPFC***			*↑ right medial temporal gyrus***	*May represent an intermediate phenotype for schizophrenia.* *Posterior ToM regions might be*

							inefficiently hyperactivated.
Park et al., 2016	*20 (17)* *Two or more relatives with schizophrenia,* *SIPS, CAARMS*	*Implicit facial emotion recognition task (explicit – gender recognition). Emotions: fearful, happy, neutral.*	*↓ frontal cortex (during fearful conditions) *** *↓ IFG and PFC (during neutral conditions) ***		*↓ amygdala*** *(fearful conditions)* *↓ amygdala complex* *(neutral conditions) ***	*↓ right middle temporal gyrus*** *↓ right STG*** *↓ fusiform gyrus* *(fearful conditions) *** *↓ fusiform gyrus*** *↓ middle temporal gyrus*** *↓ hippocampal complex* *(neutral conditions) ***	*Neural correlate of inefficient executive control for decoding of rather ambiguous facial stimuli.* *Aberrant emotional processing across brain regions including amygdala in response to ambiguous social stimuli may indicate a genetic liability for psychosis.* *Abnormal emotional processing may not be limited to amygdala, but include broad areas related to social brain circuitry.*

Marjoram et al., 2006	*12 (13)* *Two or more relatives with schizophrenia,* *PSE*	*Visual Joke Theory of Mind Task (ToM condition requires the attribution of false belief, ignorance or deception).*	*↑ bilateral medial frontal gyrus*				*Compensatory overactivation from additional systems.*
Li et al., 2012	*12 (12)* *Siblings, no SCID-NP diagnoses*	*Facial Emotional Valence Discrimination Task. Emotions: happy, fearful, neutral.*	*↑ right SFG**				*Compensatory brain mechanisms activated.*
Dodell-Feder, DeLisi, & Hooker, 2014	*19 (19)* *Siblings, no SCID/SIPS diagnoses*	*Person Description ToM task.* *False-Belief ToM task.*	*↓ right vmPFC*** *↓ OFC* *(emotion vs judgement contrasts) ***			*↓ TPJ* *(thoughts/emotions vs physical appearance) ***	*Genetic vulnerability manifests as disruption to brain regions recruited for ToM tasks.*
Rasetti et al., 2009	*29 (20)* *Siblings, no SCID diagnoses*	*Face matching task. Emotions - angry, afraid.*			*No differences in amygdala responses between the groups.*		

Barbour et al., 2010	*19 (25)* *Offspring, no SCID diagnoses*	*Continuous n-back affective task. Emotions: happy, angry, fearful, sad, neutral.*			*↓ left amygdala* *(positively valenced stimuli) **		*The decreased amygdala response may be related to a decrease in the salience of positively valenced stimuli.*

* significant at p<0.005 or p<0.001 uncorrected
** significant at p < 0.05 corrected

Table 3. Summary of included papers investigating CHR samples.
Blue shading – decreased activity. Grey shading – increased activity. Orange shading – mixed results.

Study ***(year)***	***Sample size*** ***(healthy controls)*** ***Measure***	***Task***	***Frontal cortex*** *(Risk group vs controls)*	***Cingulate cortex*** *(Risk group vs controls)*	***Limbic regions*** *(Risk group vs controls)*	***Lateral temporal cortex*** *(Risk group vs controls)*	***Conclusions***
Balevich, 2017	*28 (32)* *SPD (SCID-I)*	*Affective picture processing task. Stimuli – unpleasant, pleasant and neutral pictures, social in nature (social interactions or faces). Response – categorise stimuli.*		*↑ ACC (novel unpleasant stimuli) *****			*Increased ACC activation could either contribute to this heightened arousal or reflect an effort to regulate it.*
Gee, 2015	*200 (129)* *SIPS*	*Emotional faces task. Emotional expressions – fear, anger happy, surprised. Affect labelling and matching; gender labelling and matching; shape matching.*	*↓ vlPFC during affect conditions***	*↑ ACC***	*↓ amygdala***		*Increased ACC activity (or less of a deactivation) may relate to the process of matching affective stimuli.* *May relate more to the cognitive processes involved in*

							processing complex emotions. *Decreased amygdala activation may be specific to deficits in processing emotional stimuli when attention is directed toward the affective features.*
Brüne et al., 2011	*10 (26)* *SOPS, BLIPS*	*ToM task*		*↑ PCC**		*↑ TPJ** *↑ STG** *↑ middle temporal gyrus*	*The greater activation may represent compensatory overactive brain regions.*

Stanfield et al., 2017	*20 (32)* *SPD (SCID-II)*	*Social Judgement Approachability Task. Social cognition – face stimuli presented during approachability judgements or gender judgements.*	*↑ right inferior frontal gyrus when making social decisions*		*↑ amygdala* *(social decision conditions)*		*May represent a compensatory mechanism.* *Hyperactivation in the amygdala may represent an exaggeration of the threat response.*
Takano et al., 2017	*17 (20)* *SIPS*	*Theory of Mind Task – control, first order false belief, second order false belief (i.e. social emotion inference).*	*↓ IFG (social emotion inference conditions) **			*↑ left STG* *(during social emotion inference conditions) **	*Deficits in inferring others' social emotions.*
Mirzakhanian, 2010	*10 (12)* *SIPS*	*Emotion-Face matching Task. Emotions: angry, fearful, happy.*	*↑ right middle frontal gyrus (angry conditions) **		*No significant differences were found between prodromal populations and controls in amygdala activation*	*↑ left fusiform gyrus* *(angry conditions) **	*Abnormalities in frontal brain regions might be trait-like changes.* *Abnormalities in temporal brain regions might be trait-like changes.*

Pelletier-Baldelli, Orr, Bernard, & Mittal, 2018	*19 (20)* *SIPS*	*Social Rewards Task – passive viewing task. Face stimuli: either people who gave them positive social feedback or ambiguous social feedback.*	***Positive correlation** between vmPFC activity and greater reporting of social anhedonia***				*Individuals who experience positive feedback as unpleasant report a greater level of social anhedonia.* *An increased exchange of information between the ventral stiatum and vmPFC in clinical high risk implies down-regulation of reward response behaviour.*

Seiferth et al., 2008	*12 (12)* *BLIPS, PAANS, SCID*	*Facial Emotions for Brain Activation Task. Emotions: happy, sad, angry, fearful, neutral.*	*↑ IFG*** *↑ SFG* *(neutral relative to emotional stimuli) ***		*↑ thalamus* *(neutral vs emotional stimuli) ***	*↑ right fusiform gyrus*** *↑ hippocampus* *(neutral vs emotional stimuli) ***	*Hypersensitivity to affectively irrelevant stimuli in brain areas relevant for affective salience/significance of stimuli. Alternatively, hyperactivation to neutral stimuli may point to neural changes before illness onset.* *Stronger reactivity in regions associated with visual stimuli and face processing is consistent with the notion of altered brain function already present in perceptual pathways.*

Wolf et al., 2015	*260 (220)* *PS-R, KSADS-PL*	*Emotion identification Task. Conditions: threatening (anger and fear), nonthreatening (happy and sad).*	*↑ right middle frontal gyrus (threatening stimuli) *** *↓ deactivation in bilateral SFG***		*↑ amygdala (threatening stimuli) *** *↓ left insula***	*↑ left fusiform gyrus***	*Abnormal activity in circuitry underlying emotional processing.* *Amygdala hyperactivity may increase the likelihood of paranoid feelings or ideas.* *Subclinical illness phenotype rather than a marker of trait vulnerability.*

Modinos et al., 2015	*18 (22)* *BLIPS, CAARMS*	*Emotional processing task. Categories: negative high arousal, negative low arousal, positive high arousal, positive low arousal, neutral matched for social content.*	*↑ left IFG (neutral stimuli) *** ***Positive correlation*** *between dmPFC activity and CAARMS positive symptoms***		*↓ right amygdala*** ***Positive correlation*** *between left amygdala activation and arousal ratings to neutral pictures*** *↑ left anterior insula* *(neutral stimuli) ***		*Abnormal emotional salience engaged areas involved in more cognitive, evaluative and regulatory aspects of emotion.* *The neural correlates of abnormal salience may involve different cortico-limbic areas depending on illness stage.*

2.3.2. Summary of key findings by brain region across groups

Altogether, 32 studies reported altered activity in the frontal cortex. Of these, 18 studies reported increased activity; whereas 11 studies reported decreased activity (3 studies had mixed results). Out of the 15 studies reporting altered cingulate cortex activity, 9 studies reported increased activity. Reduced activity was found in 5 studies and 1 study reported mixed results.

Findings regarding limbic regions were particularly inconclusive with 8 studies reporting increased activity, 7 studies reporting decreased activity and 6 studies having mixed results. Findings regarding the lateral temporal cortex were similarly mixed with 8 studies reporting increased activity and 6 studies reporting decreased temporal cortex activity (2 studies had mixed results).

It is of note that out of the 39 included studies in this review, only 2 reported differences in behavioural performance between at-risk populations and healthy controls. Chan et al. (2016) reported that high schizotypy participants rated positive and neutral stimuli as less pleasant compared to controls. Similarly, CHR individuals rated neutral scenes and negative high arousal scenes as more emotionally arousing compared to controls (Modinos et al., 2015). Thus, 37 out of the 39 studies summarised here discuss differences in neural profiles in the context of similar behavioural performance.

2.3.3. Key findings in relation to SR

In relation to activity in the frontal cortex, six studies reported overall increased frontal cortex activity, three studies reported decreased activity and two studies had mixed findings. A number of studies consistently report increased activity in the dmPFC in SR samples during emotion processing (Modinos , Renken, Shamay-Tsoory, Ormel, & Aleman, 2010), during

self-reflection tasks (self vs semantic judgements contrasts, Modinos, Renken, Ormel, & Aleman, 2011) and during a second-order ToM task (Modinos et al., 2010, same sample as Modinos et al., 2011). Hyperactivation of the mPFC was also observed during emotional processing (Modinos, Renken, Shamay-Tsoory, Ormel, & Aleman, 2010) and ToM (Modinos, Ormel, & Aleman, 2010), and a positive correlation has been reported between mPFC activity and scores on anhedonia measures during the processing of social rewards (Healey et al., 2014). An investigation utilising an emotional Stroop Task found increased right middle frontal gyrus and IFG activity during negative stimuli processing (Mohanty et al., 2005). Wang et al. (2018) also reported increased middle frontal gyrus activity during a facial emotional processing task that was positively correlated with negative schizotypy scores (Wang et al., 2015). However, the same group also reported a negative correlation between activity in the middle frontal gyrus (MFG) and positive symptoms (marginally significant, Wang et al., 2015). Reduced middle frontal gyrus activation was also reported by Premkumar et al. (2013) during the processing of positive vs neutral emotional stimuli.

Findings relating to cingulate cortex activity in SR were also inconclusive, with three studies reporting increased activity in the ACC (Wang et al., 2018; Modinos et al., 2017; Modinos , Renken, Shamay-Tsoory, Ormel, & Aleman, 2010), two studies reporting decreased activity in the PCC and ACC (Huang et al., 2013; Premkumar et al., 2012) and one study reporting mixed results (Modinos, Renken, Ormel, & Aleman, 2011).

Studies that assessed activity in limbic regions reported mixed results. Inconclusively, one study reported increased insula activity (Modinos et al., 2011) and two studies reported mixed results within the amygdala, insula and the nucleus accumbens (Mohanty et al., 2005; Wang et al., 2018). The two studies that consistently reported decreased limbic regions activity

in, in the insula and thalamus, reported contrasts for positive vs neutral stimuli (Premkumar et al., 2013; Chan et al., 2016).

In relation to temporal cortex activity in SR samples, two studies reported increased activity in the bilateral medial temporal gyrus (MTG; Wang et al., 2015) and the right TPJ (Modinos et al., 2017). The only consistent finding was decreased activity in the STG during studies using emotional processing tasks (Germine, 2012; Huang et al., 2013; Premkumar et al., 2013).

2.3.4. Key findings in relation to FR

Studies in FR samples report mixed findings in relation to frontal cortex activity during social cognition, with 7 studies reporting increased activity, six studies reporting decreased activity and one study reporting no differences between FR and healthy control groups (Spilka & Goghari, 2017). Increased mPFC activity has been reported during an emotional valence rating task (van Buuren, Vink, Rapcencu, & Kahn, 2011) and during a ToM task (Marjoram et al., 2006). Increased IFG and SFG activity has been reported by two studies (de Achával et al., 2013; Spilka, Arnold, & Goghari, 2015; Li et al., 2012; Pulkkinen et al., 2015). Furthermore, positive correlations between dorsolateral PFC (dlPFC) and IFG activation and scores on the Social Skills Performance questionnaire have been reported during basic emotion processing and between SFG and medial frontal gyrus (MFG) and scores on the same questionnaire during ToM processing (Villarreal et al., 2014).

Reduced frontal cortex activity in FR samples has been reported predominantly for emotional processing tasks, with hypoactivations in the mPFC (de Achával et al., 2012; van der Meer et al., 2014; Park et al., 2016) and in the IFG and PFC during the processing of neutral

stimuli in particular (Park et al., 2016). During ToM tasks, reduced activation has been reported in lateral PFC and dmPFC (Walter et al., 2011) and in the ventromedial PFC and OFC (Dodell-Feder, DeLisi, & Hooker, 2014).

Results investigating cingulate cortex activity were inconclusive with three studies reporting increased activity in ACC and PCC (Villarreal et al., 2014; Spilka & Goghari, 2017; van Buuren et al., 2011) and two studies reporting decreased activity (Pulkkinen et al., 2015; Walter et al., 2011).

Studies reporting altered limbic region functioning in FR samples again report inconclusive results. Four studies reported increased limbic activity, whereas three studies reported decreased activity and one study reported no significant differences during an emotion face matching task (Rasetti et al., 2009). Increased insula activity has been reported during emotion processing (de Achával et al., 2012; for fearful vs. neutral contrasts, Spilka et al., 2015), and one study found a positive correlation between insula activity and Social Skills Performance ratings during a basic emotion processing task (Villarreal et al., 2014). All three studies reporting hypoactivity in limbic regions identified this pattern in the amygdala, with reduced activity found during emotion processing specifically (van der Meer et al., 2014; Park, et al., 2016; Barbour et al., 2010).

Two studies report increased temporal cortex activity, three studies reported decreased activity and one study had mixed results (Spilka, Arnold, & Goghari, 2015). Increased temporal cortex activity has been reported during an emotional processing task (van Buuren et al., 2011) and during a ToM task (Mohnke et al., 2015). Decreased STG activity has been reported for emotion processing (Park et al., 2016; van der Meer et al., 2014). Further, deactivations were observed in the TPJ for the thoughts/emotions vs physical appearance contrasts on a person-

description ToM task (Dodell-Feder, DeLisi, & Hooker, 2014), and in the MTG for the neutral conditions of an emotional task (Park et al., 2016).

2.3.5. Key findings in relation to CHR

Six studies reported increased activity in the frontal cortex and three reported decreased activity. One of the first studies investigating social cognition in CHR samples using a facial emotional task reported increased activity in the IFG and the SFG for neutral relative to emotional stimuli (emotional stimuli included happy, sad, angry and fearful; Seiferth et al., 2008). Similarly, Modinos et al. (2015) reported increased left IFG activity for neutral stimuli during an emotional processing task. Increased right MFG activity has been reported during angry (Mirzakhanian, 2010) and threatening stimuli (Wolf et al., 2015). Stanfield et al. (2017) similarly reported a trend level increase in activation in the right IFG during social decision making in a social judgement task. Furthermore, positive correlations have been reported between increased vmPFC activity and greater scores on social anhedonia symptomatology (Pelletier-Baldelli, Orr, Bernard, & Mittal, 2018) and between dmPFC activity and positive symptoms on a CHR diagnostic interview (i.e. Comprehensive Assessment of At-Risk Mental States; Modinos et al., 2015). In contrast, Gee (2015) reported reduced vmPFC activity during emotional conditions and Takano et al. (2017) reported decreased IFG activity during the social emotion inference conditions on a ToM task. Decreased activity in the bilateral SFG has also been reported during emotion identification tasks (Wolf et al., 2015).

The three studies that reported altered activity in the cingulate cortex all reported increased activity relative to healthy controls (for novel unpleasant stimuli; Balevich, 2017;

Gee, 2015) and the PCC (Brüne et al., 2011). The first two used an emotional processing task, whereas the last study utilised a ToM task.

In relation to activity in limbic regions, two studies reported increased activity (Seiferth et al., 2008; Stanfield et al., 2017), and one study reported decreased activity in the amygdala during emotion processing (Gee, 2015). Two studies reported mixed limbic activity during emotional processing tasks (Wolf et al., 2015; Modinos et al., 2015). Yet, abnormal activity was observed in relation to neutral stimuli with positive correlations between amygdala activity and arousal ratings to neutral stimuli and increased insula activity to neutral stimuli (Modinos et al., 2015).

All five studies reporting results for the lateral temporal cortex in the CHR group reported increased activity. During a ToM task Brüne et al. (2011) reported increased activity in the TPJ, the STG and the MTG. Similarly, increased activity in the left STG has been reported during social emotion inference conditions on a ToM task (Takano et al., 2017) and during an emotional processing task (Wolf et al., 2015). Increased left fusiform gyrus activity for angry stimuli during an emotional processing task were also reported by Mirzakhanian et al. (2010). Increased right fusiform gyrus (for neutral vs emotional stimuli conditions) during an emotion processing task were reported by Seiferth et al. (2008).

2.4. Discussion

This systematic review aimed to provide a greater understanding of the neurofunctional correlates of social cognition deficits in different psychosis risk populations.

The at-risk populations included in the review were individuals with schizotypal personality traits, assessed psychometrically (SR), individuals at familial/genetic risk of

psychosis (FR) and individuals at clinical high risk for psychosis (CHR). Overall, the results of this systematic review are consistent with findings in schizophrenia populations (Green, Horan, & Lee, 2015; Kring & Elis, 2013), reporting altered, both increased and decreased, functional activation in a range of cortical and subcortical regions during social cognition tasks. However, within this broader picture, there are some consistent findings. Most studies in at-risk populations report increased activations in the frontal cortex and, all studies report that CHR populations are characterised by increased activity in the lateral and medial temporal cortex during social cognition task. This is consistent with studies indicating that psychosis may emerges from dysfunction in medial temporal and frontotemporal regions due to increased excitatory neurotransmission (Allen et al., 2019). However, for cingulate and limbic regions activation patterns are more difficult to interpret across at-risk populations, with both increased and decreased functional activation seen during a range of social cognition tasks. Below we discuss our findings according to brain regions.

2.4.1. Frontal and cingulate cortices

Various prefrontal regions reliably showed differential activations in at-risk groups during social cognition tasks. The mPFC, vl/vmPFC, MFG, IFG and SFG show both increased and decreased patterns of activation in both SR populations (Healey et al., 2014; Mohanty et al., 2005; Wang et al., 2018; Wang et al., 2015; Modinos, Ormel, & Aleman, 2010; Modinos, Renken, Shamay-Tsoory, Ormel, & Aleman, 2010; Modinos, Renken, Ormel, & Aleman, 2011) and in CHR populations (Seiferth et al., 2008; Modinos et al., 2015; Mirzakhian 2010; Wolf et al., 2015; Stanfield et al., 2017; Pelletier-Baldelli et al., 2018).

Neuroimaging studies have implicated the mPFC in inferring the internal states and intentions of others, in regulating emotion, in processing reward and punishment and in the

contextual interpretation of complex social information (Phan, Wager, Taylor, & Liberzon, 2002). The consistent patterns of increased activity in the mPFC in at-risk populations during social cognition tasks might represent abnormal processing of socially salient cues leading to abberant beliefs about others and thus contributing to the formation of delusions (Morrison et al., 2004).

Yet, several studies in at-risk populations (Gee, 2015; Takano et al., 2017; Dodell-Feder, DeLisi, & Hooker, 2014; de Achával et al., 2012) and patients with schizophrenia (Russell et al., 2000; Eack, Wojtalik, Newhill, Keshavan, & Phillips, 2013; Lee, Quintana, Nori, & Green, 2011; Dodell-Feder et al., 2014) also report findings of decreased frontal cortex activity that may be specifically related to mentalising deficits (Savla et al., 2007). Furthermore, based on the finding reported here, no definite conclusions can be drawn regarding activity in the cingulate cortex in SR and FR groups, regardless of the type of social cognition task. However, CHR groups do demonstrate a consistent pattern of increased activity in the ACC and the PCC during both emotional processing and ToM, respectively (Balevich, 2017; Gee, 2015; Brüne et al., 2011). The ACC is involved in a variety of both affective and cognitive functions, such as conditioned emotional learning, assessment of motivational context and integrating emotional information to motivate behaviour (Devinsky, Morrell, & Vogt, 1995; Fig 1). Consequently, increased ACC activity in CHR groups may be related to abnormal salience processing such that increased activity is either contributing to a general heightened state of arousal or is part of an effort to regulate it (Gee, 2015; Balevich, 2017). Functional disruptions in the ACC have been widely implicated in the illness progress of schizophrenia with gradual changes in grey matter volume in the ACC region of the salience network predictive of conversion to psychosis (Palaniyappan & Liddle, 2012).

Overall, the results in at-risk groups suggest that there is a subnetwork of areas in frontal and ACC regions that are differentially activated in at-risk populations. This pattern of abnormal neural activity supports the notion that the processing of social cues is dysfunctional at the earliest stages of the schizophrenia continuum, and that both the recognition/response to social-affective stimuli and the ability for higher order inferences about social information are impaired.

2.4.2. Lateral temporal and limbic regions

Lateral regions of the temporal cortex also showed increased activation patterns during social cognition tasks in at-risk populations. Increased activity in the TPJ and the STG are reported in CHR populations during ToM tasks and during emotional processing (Brüne et al., 2011; Takano et al.; 2017; Wolf et al., 2015; Mirzakhanian, 2010; Seiferth et al., 2008). These regions of the temporal cortex are important for inferring the intentions of others, for recognising nonverbal social cues and for representing non-verbal social cues with emotional content (Ochsner, 2008). Collectively, these results support the notion that increased neural activity in the lateral temporal cortex is associated with abnormal processing of emotional and social information in CHR samples (Seiferth et al., 2008) as well as emotion processing and mentalising (i.e. TPJ, STG; Shamay-Tsoory et al., 2007; Pinkham, Gur, & Gur, 2007).

The medial temporal network (including areas in amygdala, hippocampus) along with the ventral striatum has been heavily implicated in the progression of psychosis (Modinos et al. 2015; Allen et al., 2019). However, results in relation to these regions were inconclusive in all three at-risk groups (see Results section). Interestingly, some single studies utilising emotional processing tasks in CHR participants have reported increased activity in response to neutral stimuli in the insula (Modinos et al., 2015) and the thalamus (Seiferth et al., 2008). The

insula, particularly the anterior part, has been implicated in the evaluative, experiential or expressive processing of internally generated emotions (Reiman et al., 1997; Craig & Craig, 2009). The thalamus (particularly the pulvinar thalamus and the superior colliculus) has also been identified as a key region for emotion processing due to its role as a robust excitatory pathway controlling emotional attention through a projection from the amygdala (Pessoa & Adolphs, 2010; Phillips, Drevets, Rauch, & Lane, 2003; Adolphs, 2002). This pattern of increased activity to neutral stimuli in regions involved in affective salience and attention processing suggests a neural hypersensitivity to affectively irrelevant stimuli and may be related to aberrant salience processing. This pattern of activation in psychosis risk groups is broadly consistent with hyperactivation in limbic regions in response to neutral stimuli that has been reported in patients with chronic schizophrenia (Holt et al., 2006; Surguladze et al., 2006; Hall et al., 2008).

Furthermore, studies have reported abnormal activity in other temporal lobe regions such as the MTG, the fusiform gyrus and the hippocampus in CHR groups during ToM and emotional processing task (Brüne et al., 2011; Takano et al.; 2017; Wolf et al., 2015; Mirzakhanian, 2010; Seiferth et al., 2008). Collectively, these results support the notion of abnormal processing of emotional and social information in CHR samples. These results appear to be in line with evidence of hippocampal and medial temporal cortex dysfunction during the emergence of psychosis (Allen et al., 2018; Allen et al., 2016; Lodge & Grace, 2011; Modinos et al., 2018). Recent evidence suggests that this pattern of hippocampal hyperactivity in psychosis and psychosis risk groups is associated with the dysregulation of striatal dopamine (Lodge & Grace, 2011; Modinos, Allen, Grace, McGuire 2015) which may also affect salience processing (Winton-Brown et al., 2014). Moreover, another major implication of phasic dopamine dysfunction is its effect on synaptic plasticity. Patients with schizophrenia present with reduced connectivity across neural regions and networks (i.e. reduced interaction between

neural regions) and this has been proposed to result from a disturbance in NMDAR-dependent synaptic plasticity (Stephan, Diaconescu, & Iglesias, 2016; for a review see Stephan, Friston, & Frith, 2009). Neuromodulatory transmitters, such as dopamine, exert a regulatory effect on NMDAR-dependent synaptic plasticity, thus the aberrant regulation of dopamine could lead to abnormal functional integration across brain regions in patients with, and at-risk of psychosis (Diaconescu, Hauke, & Borgwardt, 2019) including in regions important for processing of social information..

In particular, dopamine dysregulation in the ventral striatum may leads to reduced gating of information flow from prefrontal areas and a failure to fully engage optimal cognitive regulation (Grace, 2000). Impairment of this mechanism could lead to abnormal processing of social and emotional information and to the formation of delusions (Mohanty et al., 2005; Liddle, Lane, & Ngan, 2000). This idea is consistent with the neuroimaging findings from the current systematic review indicating increased activity in prefrontal regions for the processing of neutral relative to valenced stimuli. In CHR population, Modinos et al. (2015) reported increased activity in the IFG in response to neutral stimuli during an emotional processing task. Similarly, Seiferth (2008) reported increased activity in the IFG and the SFG for neutral relative to emotional stimuli in a facial emotional processing task. All CHR studies included in the current review reported neural hypersensitivity to neutrally valenced stimuli in both temporal and frontal lobe regions. Taken together, the results support models that posit widespread over activity to neutral stimuli possibly due to hyperactivity of the striatal dopamine system (Lodge & Grace, 2011; Grace, Floresco, Goto, & Lodge, 2007).

2.4.3. Conclusions and future directions

Overall, the studies reviewed here consistently show neural activity differences between specific at-risk groups and healthy controls during social cognition tasks. The most predominant findings are observed in frontal cortex where neural hyperactivity in SR and CHR groups is widely reported, indicating impairments in circuits involved in the processing of emotional stimuli. Furthermore, CHR samples were characterised by abnormal responses to neutral stimuli (across all tasks) and hyperactivity in the ACC and temporal lobe regions. These results suggest that CHR samples might present with emerging dysfunction across frontal and temporal regions that may impair salience processing. These findings are in line with recent conceptualizations in schizophrenia, indicating that hyperactivity and dysfunction, particularly in medial temporal regions, lead to dopamine dysregulation, aberrant salience and delusional ideation. It is known that regions implicated in the neuropathology of schizophrenia (i.e. fronto-striatal circuits, limbic areas, ACC, medial and lateral temporal regions) receive innervation from the limbic hippocampus (Grace & Gomes, 2018; Heinz et al., 2018). Thus, the abnormal medial temporal cortex functioning observed across many studies may have far-reaching consequences for information processing by disrupting related circuits and influencing higher level (social) cognition (Calcia et al., 2016; Powers, Mathys, & Corlett, 2017). However, no consistent activity patterns were seen for limbic and cingulate regions across at-risk groups, furthermore the results in FR samples were highly inconsistent.

It should be noted that, alternatively, increased frontal cortex activity could represent compensatory mechanisms during the processing of social information to allow for the same level of behavioural performance. Indeed, the studies in at-risk groups reviewed here showed that SR, FR, CHR participants did not significantly differ from the healthy controls on behavioural measures of social cognition, although widespread differences in neural activity

were observed. Higher activity in prefrontal regions during ToM could mean that at-risk groups require greater effort to utilise cognitive operations during mentalization to attain a behavioural performance similar to controls (Modinos, Renken, Shamay-Tsoory, Ormel, & Aleman, 2010). Similarly, greater activation in prefrontal regions might represent a compensatory mechanism such that higher cognitive control is required to down-regulate the experience of negative emotions (Modinos, Ormel, & Aleman, 2010; Wang et al., 2018). In contrast, a general pattern of decreased frontal activity (which is associated with impaired behavioural performance, Green et al., 2015) might be indicative of a generalized cognitive impairment. Indeed, some of the networks identified by the studies included in this review are also heavily implicated in general cognition and are responsible for cognitive processes in the broader sense. Medial frontal regions are implicated in wide range of cognitive operations, such as conflict monitoring, error detection, executive control, reward-guided learning and decision-making (Ridderinkhof, Ullsperger, Crone, & Nieuwenhuis, 2004; Euston, Gruber, & McNaughton, 2012; Bechara & Damasio, 2005). Lateral (Buchsbaum, Olsen, Koch, & Berman, 2005; Rauschecker & Scott, 2009) and medial temporal regions (Squire & Zola-Morgan, 1991; Alvarez & Squire, 1994) have been associated with auditory and memory functions, respectively. Discussing impairments in general cognition is beyond the scope of the current review, but future studies should attempt to utilise task paradigms that allow the disassociation of neural patterns associated with social cognition and general cognitive control and/or mnemonic processes.

A caveat of the review is that even though the majority of the discussion relates to the direction of neural activity observed during social cognition tasks, this might simply be a reflection of basal state activation in these at-risk populations. A few studies suggest that SR and CHR populations present with increased resting perfusion, particularly in the hippocampus, midbrain and basal ganglia (Allen et al., 2018; Allen et al., 2016; Modinos et al.,

2018). Medication might also affect the fMRI findings reported here, but this was relevant only to a very small subset of the CHR studies and thus not likely to make a difference in the overall interpretation of the neural patterns observed. Finally, there appears to be no associations between level of risk for psychosis and altered activity during a particular social cognition heuristic (i.e. ToM tasks, emotional processing tasks), However, this might be because the majority of studies utilised lower level social cognition tasks (i.e. emotion recognition, emotional valence discrimination). One pattern that does emerge however, is that at-risk populations show aberrant processing of salience in relation to emotional stimuli, in frontal (SR and CHR), and cingulate cortices (CHR), and an abnormal responses to neutral stimuli in both temporal and frontal lobe regions (CHR).

Chapter Three

Aims and Methodology

3.1. Social Cognition

3.1.1. Existing gaps in knowledge

As outlined by the systematic review of the literature, studies have shown that schizotypy individuals present with abnormal neural activity during social cognition tasks (mainly patterns of increased frontal cortex activity; Kozhuharova, Saviola, Ettinger, & Allen, 2020). The majority of studies report these abnormal neural patterns are evident in the absence of any behavioural differences on task performance related to ToM or emotion recognition (Kozhuharova et al., 2020). However, there is limited knowledge of the learning mechanisms that drive social decision making in schizotypy samples and whether specific aspects of these learning mechanisms can explain the abnormal neural patterns observed.

Despite a number of previous studies reporting social cognitive deficits measured with tasks assessing emotion processing (Edwards, Jackson, & Pattison, 2002; Kohler & Brennan, 2004; van't Wout, Aleman, Kessels, Cahn, de Haan, & Kahn, 2007), ToM (Corcoran, Mercer, & Frith, 1995; Greig, Bryson, & Bell, 2004), social perceptions and judgements (Baas, van't Wout, Aleman, & Kahn, 2008; Corrigan & Green, 1993; Toomey, Schuldberg, Corrigan, & Green, 2002) and social knowledge or understanding social schema (Corrigan & Addis, 1995; Penn, Ritchie, Francis, Combs, & Martin, 2002), currently very little is known about the mechanisms driving learning from socially salient cues, i.e. how prediction errors and uncertainty levels influence learning from social cues. To this end, we employed a modified version of a well-validated belief updating task to allow us to measure the neural correlates

associated with socially salient (vs non-social) prediction errors in at-risk populations. We also employed a social probabilistic learning task to investigate if the basic perceptual and learning processes underlying social decision making are impaired in schizotypy samples. From a computational perspective, this task also allows us to measure if and to what extend social information influences decision making behaviour.

3.1.2. Aims and objectives for social cognition

The current thesis involved two separate tasks to investigate the neural correlates of social cognition in high schizotypy samples in comparison to low schizotypy samples, a modified belief updating task (Garrett et al., 2014; Kuzmanovic, Jefferson, & Vogeley, 2015; Kuzmanovic, Jefferson, & Vogeley, 2016; Sharot, Korn, & Dolan, 2011) and a social probabilistic learning task (Sevgi, Diaconescu, Henco, Tittgemeyer, & Schilbach; 2020). The first task allowed us to compare judgements referring to social events with those about non-social events to investigate if schizotypy traits affect the way participants update their beliefs when the event is socially salient, i.e. whether learning varies with changes in the social nature of the events. To this end, we investigated the neural substrates that track prediction errors in response to social/non-social events in high vs low schizotypy individuals.

The second task allows us to directly compare learning signals from social and non-social information in a computational framework, i.e. we investigated the effects of prediction errors and uncertainty and how these computational quantities affect decision making directly. More specifically, we investigated if high schizotypy presents with putative abnormalities during learning and decision making under environmental uncertainty (volatility). The task required that participants learn simultaneously from the social and the non-social cues allowing us to precisely measure the computational parameters driving learning. Further, the task allows

the measurement of the weight on the precision of the social vs non-social cue on decision making, i.e. whether participants are more likely to follow social or non-social cues when making probabilistic decisions. The use of functional magnetic resonance imaging (fMRI) alongside this task will allow us to investigate group differences between high and low schizotypy samples in brain activity corresponding to learning signals. Combined, these tasks will give a comprehensive overview of the specific learning signals that are impaired during social learning in schizotypy samples along with the precise neural signature of these abnormal social learning models.

3.1.3. Hypotheses for social cognition

We used the belief updating task in combination with fMRI to examine whether high schizotypy traits are associated with neural responses that are likely to support a more biased integration of information about social future events. We hypothesise that, behaviourally, we will replicate previous studies and report an optimism bias across the sample (i.e. people update beliefs more for desirable compared to undesirable events; (Garrett et al., 2014; Garrett & Sharot, 2017; Sharot et al., 2011; Sharot, Guitart-Masip, Korn, Chowdhury, & Dolan, 2012; Sharot & Garrett, 2016). We expect to find more updating in social vs non-social conditions, in line with previous research indicating that social information is of particular importance for people over and above non-social information (Adolphs, 2001; Adolphs, 2003a; Adolphs, 2003b; Adolphs, 2009). We predict that there will be no behavioural differences between high and low schizotypy individuals in terms of behavioural responses to the task (i.e. updating) due as reported in previous reviews (Kozhuharova et al., 2020). We predict, whilst behavioural performance is unaltered, HS individuals will show abnormal prefrontal cortex activity in response to social prediction errors. Because previous work has shown that high schizotypy

traits are associated with increased activity in the prefrontal cortex, compared to healthy controls, in response to social tasks (Kozhuharova et al., 2020; Modinos, Renken, Ormel, & Aleman, 2011; Mohanty et al., 2005) and with altered activity in a fronto-striatal network responding to nonsocial prediction errors (Corlett & Fletcher, 2012), we hypothesis that relative to low schizotypy (LS) participants, high schizotypy (HS) participants will show increased activity in prefrontal and striatal regions during social belief updating.

Using a social learning probabilistic task, we aimed to further investigate hierarchical learning from social information in HS subjects. The task will allow us to examine if HS subject put more weight on social vs non-social information or whether they learn equally from these cues. We will further investigate how HS subjects learn under conditions of uncertainty. In line with previous work in hierarchical learning under volatility in CHR individuals (Cole et al., 2020) and schizophrenia patients (Adams, Stephan, Brown, Frith, & Friston, 2013; Powers et al., 2017; Woodward, Moritz, Cuttler, & Whitman, 2006) we hypothesise that HS will present with abnormal mechanisms for processing uncertainty and volatility. Similar to neural investigations of learning in CHR samples, we expect that HS subjects will further present with abnormal neural processing of key learning parameters such as prediction errors (Cole et al., 2020).

3.2. Testing the MAM model in schizotypy (methylazoxymethanol acetate model)

The sample design was well suited to inform on schizotypy as representing the earliest risk for schizophrenia-spectrum conditions. We enlisted only the top 10% and the bottom 10% of schizotypy scorers in order to be able to extrapolate findings to patterns in high schizotypy samples (high on all 3 subfactors combined). The high scoring schizotypy group serves as a

useful cohort to compare the earliest stages of psychosis risk and draw comparisons with previous findings in at-risk and schizophrenia populations. Due to this specific design characteristics, we further utilised Magnetic Resonance Spectroscopy (MRS) and resting state fMRI (rs-fMRI) to test some of the key assumptions of the methylazoxymethanol acetate (MAM) animal model of psychosis in population with elevated risk for the illness (Lodge, Behrens, & Grace, 2009). This model is well established and posits a disruption of brain development, which is thought to be fundamental to the development of psychotic disorders (Flagstad et al., 2004; Grace & Moore, 1998; Moore, Jentsch, Ghajarnia, Geyer, & Grace, 2006). Fundamentally, the MAM model provides a mechanistic explanation of how elevation in dopamine function leads to the formation of abnormal associations and underlies the generation of symptoms such as delusions (Lisman, Grace, & Duzel, 2011; Lisman & Grace, 2005, Fig 1). Yet, some of its key assumptions have not been tested in a sample at the extreme end of the schizotypy continuum.

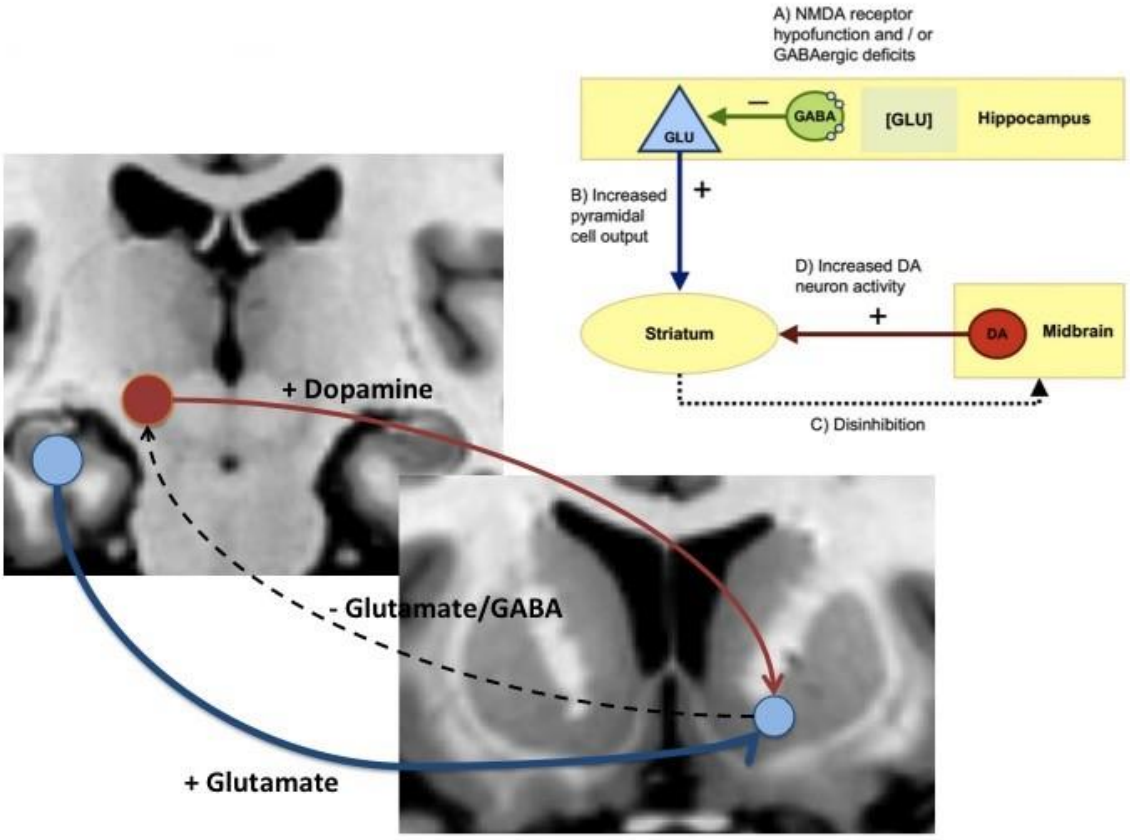

Fig 1. Diagram showing hippocampal midbrain striatal circuit involved in the regulation of striatal dopamine via glutamatergic, GABAergic projections (+) = excitatory pathway and (−) = inhibitory pathway. In schizophrenia and clinical high-risk (CHR) states, it is hypothesized that increased glutamatergic output from the hippocampal subiculum to the ventral striatum (blue pathway) reduces inhibition via glutamatergic and GABAergic pathways that ultimately drives ventral tegmental area (VTA) dopamine cells and dopamine release back to the striatum (red pathway).

Gestation administration of MAM leads to selective histopathology in the mediodorsal thalamus, hippocampus, parahippocampal and prefrontal cortices of adult rats (regions specifically associated with schizophrenia pathology; (Gastambide et al., 2012; Moore et al., 2006), which might be due to a specific reduction of parvalbumin positive GABAergic interneuron numbers in these regions (Lodge et al., 2009). Decreases in parvalbumin expression might also affect certain classes of cortical GABA interneurons known to be reduced in schizophrenia populations (Akbarian et al., 1995). Indeed, post-mortem research has demonstrated reduced density of fast-spiking parvalbumin-positive interneurons in a

corticolimbic circuitry involving the prefrontal cortex (PFC) in schizophrenia (Akbarian & Huang, 2006; Benes, 2010; Lewis, Hashimoto, & Volk, 2005). Crucially, administration of MAM leads to elevated striatal dopaminergic activity and over-activity in reciprocal signalling pathways between the MTL and striatum (Lodge & Grace, 2007). This overactivation stimulates GABAergic neurons projecting from the striatum to the ventral pallidum leading to disinhibition of midbrain dopaminergic neurons and the increase in the release of dopamine in the striatum. In turn, the dopaminergic neurons in the midbrain project back to the striatum and the hippocampus, producing further disinhibition and forming a positive feedback loop (Hammad & Wagner, 2006).

A number of different concepts from the MAM model have been tested in schizophrenia patients and CHR populations, with data being consistent with the model predictions. Schizophrenia patients present with increased subcortical dopamine synthesis and release (Abi-Dargham, 2004; Davis, Kahn, Ko, & Davidson, 1991; Howes, Egerton, Allan, McGuire, Stokes, & Kapur, 2009; Laruelle et al., 1996; Lindström et al., 1999; Mackay et al., 1982). Elevated dopamine function in the striatum and the midbrain has also been documented in CHR populations, particularly in the subgroup that subsequently develops a psychotic disorder (Allen et al., 2012; Howes et al., 2011). Structural MRI studies have confirmed reductions in MTL volume in both schizophrenia patients (Abi-Dargham, 2004; Honea, Crow, Passingham, & Mackay, 2005; Kapur, Mizrahi, & Li, 2005; Seamans & Yang, 2004; Shenton, Gerig, McCarley, Szekely, & Kikinis, 2002; Steen, Mull, Mcclure, Hamer, & Lieberman, 2006; Wright et al., 2000), and in CHR populations (Borgwardt et al., 2007; Hurlemann et al., 2008; Phillips et al., 2002; Witthaus et al., 2010; Wood et al., 2005; Wood et al., 2010), with the latter demonstrating significant reductions in hippocampal grey matter specifically. Studies using fMRI have confirmed altered MTL activity at rest in schizophrenia patients (Andreasen et al., 1997; Horn et al., 2009; Malaspina et al., 2004; Pinkham et al., 2011; Scheef et al., 2010) and

increased resting state cerebral blood volume in the CA1 region of the hippocampus in CHR individuals who transitioned to psychosis (Schobel et al., 2009). Longitudinal follow-up in this cohort showed that the onset of psychosis was associated with a progressive increase in hippocampal cerebral blood volume (Schobel et al., 2009). This increased hippocampal neural activity is believed to lead to the dysregulation of striatal-midbrain dopamine signalling (Gomes & Grace, 2016; Lodge & Grace, 2011) through a hippocampal-striatal-midbrain circuit. Further, longitudinal studies in CHR groups showed that normalization of hippocampal resting cerebral blood flow tracked with clinical improvement of symptoms, while elevated hippocampal resting cerebral blood flow persisted in those who remained symptomatic or developed psychosis (Allen et al., 2016).

Resting state functional studies of hippocampal connectivity in schizophrenia and CHR samples support the notion that the hippocampus is a key region in the symptomatology and progression of schizophrenia-spectrum disorders. Studies have reported that the hippocampus show reduced functional connectivity with distributed brain regions during rest in schizophrenia (Liang et al., 2006; Zhou et al., 2007) including the bilateral putamen region within the striatum (Kraguljac, Nina Vanessa, White, Hadley, Reid, & Lahti, 2014). Reduced resting state connectivity between the hippocampus and thalamus have also been reported in a large sample of schizophrenia patients compared to controls (Samudra et al., 2015) and CHR studies have also found a significant decrease in the strength of the intrinsic connectivity between the hippocampal formation and the inferior frontal gyrus (Benetti et al., 2009).

The MAM animal model suggests that people with an elevated risk of psychosis, or in the early stages of a psychotic disorder, would be expected to show, relative to healthy controls: increased glutamate levels in the cortex, MTL and striatum, increased cortical glutamate levels and reduced cortical and MTL GABA levels. Moreover, the role of GABA in the development

of psychosis is further supported by preclinical evidence that peripubertal (i.e., premorbid) pharmacological intervention on certain GABA receptors prevents schizophrenia-like GABA cell loss and blocks the development of psychosis-like features in adult rats (Du & Grace, 2013; Du & Grace, 2016). According to the MAM model, cortical glutamate levels are increased due to a reduction in GABAergic inhibition of local pyramidal neurons (Lisman & Grace, 2005). However, MRS studies in patients with schizophrenia have reported both increased and decreased cortical glutamate levels. Decreases have been described in the medial prefrontal cortex (Marsman et al., 2013), whereas increases have been reported in the hippocampus (Kegeles et al., 2000). Most studies in unmedicated first episode psychosis patients have found elevated glutamate and glutamine levels in the hippocampus, anterior cingulate and thalamus (Kraguljac, White, Reid, & Lahti, 2013; Théberge et al., 2002). This potentially confusing set of findings may partly reflect a variation in the nature of alterations in glutamate levels according to the stage of psychotic illness (Marsman et al., 2013).

The MAM model also predicts that cortical GABA levels should be decreased in psychosis due to loss and dysfunction of inhibitory GABAergic interneurons. Both the uptake (Reynolds, Czudek, & Andrews, 1990; Simpson, Slater, Deakin, Royston, & Skan, 1989) and release (Sherman, Davidson, Baruah, Hegwood, & Waziri, 1991) of GABA have been reported to be reduced in cortical synaptosomes prepared from schizophrenic subjects. In the PFC, the activity of glutamic acid decarboxylase, the synthetic enzyme for GABA, is reduced in subjects with schizophrenia (Mackay et al., 1982; Sherman et al., 1991) as is the expression of the mRNA for this enzyme (Akbarian et al., 1995; Huang & Akbarian, 2007). In addition, ligand binding studies have revealed abnormalities in PFC GABA receptors in schizophrenia (Benes, Vincent, Marie, & Khan, 1996).

3.2.1. Existing gaps in knowledge

Crucially, research investigating GABA and glutamate in high schizotypy samples is very limited. Such studies are however, of great interest, as animal models of psychosis propose a dysfunction of these metabolites in the progression of the disorder. The one previous study investigating glutamate levels in individuals scoring high on the positive schizotypy scale only, in comparison to low positive schizotypy, reported no differences in glutamate levels between the groups in the anterior cingulate cortex, but there was an interaction effects such that glutamate levels were negatively associated with the degree of activation to emotional pictures in the striatum and the mPFC (Modinos et al., 2017). These preliminary findings suggest that cortical glutamate levels might be impaired in high (positive) schizotypy, yet to date there is no direct investigation of this hypothesis in total high schizotypy across all three subfactors.

Furthermore, abnormal functioning of midbrain regions is a key assumption of the MAM model. Recent rs-fMRI studies have reported that the positive dimension of schizotypy is positively associated with ventral striatal-PFC connectivity and negatively associated with dorsal striatal-posterior cingulate connectivity (Wang, Ettinger, Meindl, & Chan, 2018), and higher total schizotypy score has been associated with lower ventral striatal connectivity (Rössler et al., 2018). Similar findings were obtained using multi-echo rs-fMRI methodology where subjects scoring high on the positive dimension of schizotypy, compared to those scoring low on this dimension, showed lower resting state functional connectivity between ventromedial prefrontal regions and ventral striatal regions; and between the dorsal putamen and the hippocampus (Waltmann et al., 2019). While the literature dependably reports abnormal striatal connectivity in the progression of schizophrenia spectrum disorders, only one previous study has examined hippocampal-striatal resting functional connectivity (Waltmann et al., 2019) and this study utilised a sample high only on the positive dimension of schizotypy

personality traits. Thus, it is unclear if abnormal striatal functioning is associated with dysregulation of hippocampus-striatal regions in relation to the negative and disorganised traits of schizotypy as well. No previous studies have investigated if the hippocampus, a region suggested by the MAM model to be critical for psychosis progression, has abnormal connectivity in high schizotypy individuals.

3.2.2. Aims and hypotheses for testing the MAM model

The aim of our rs-fMRI study is to conduct the first investigations of resting state functional connectivity patterns between the hippocampus, striatum and prefrontal regions in a high (relative to a low) schizotypy sample. Based on the importance of hippocampal activity in the progression of psychosis (Allen et al., 2019; Grace, 2016; Lodge & Grace, 2011) we chose the hippocampus as a seed region and examined connectivity patterns with the striatum, thalamus and prefrontal cortex. We chose to include the thalamus as a region of interest (ROI) as the prefrontal cortex receives striatal output via the thalamus (Haber, 2016), thus abnormal striatal functioning could affect thalamus activity. Furthermore, abnormal function of the PFC-thalamic-striatal loop is theorised to account for a number of schizophrenia symptoms such as psychosis and cognitive deficits (Howes, Egerton, Allan, McGuire, Stokes, & Kapur, 2009). We expect that in HS groups the hippocampus will show reduced functional connectivity with the striatum, thalamus and PFC regions.

The aim of our MRS study is to investigate glutamate and GABA levels in a sample of high schizotypy, compared to low schizotypy, using MRS from a voxel located in the medial PFC. The voxel selection was informed based on the mPFC's implication in animal models of psychosis suggesting that cortical glutamate and GABA levels should be reduced in schizophrenia (Mailly, Aliane, Groenewegen, Haber, & Deniau, 2013; Modinos, Allen, Grace,

& McGuire, 2015) and findings of mainly decreased levels in the mPFC of patients (Egerton et al., 2017; Marsman et al., 2013). We predict reduced levels of glutamate and GABA in high schizotypy individuals compared to low schizotypy.

3.3. Methodology

The current thesis utilised MRI imaging techniques and computational models to address the research questions outlined above. The timeline of the MRI scanning protocol for all participants was as follows: i) localizer and structural scans (~ 3min), ii) belief updating fMRI task (2 runs each ~ 12min), iii) MRS scan (~ 13 min), iv) social probabilistic fMRI task (~22min), v) resting state fMRI (~10min).

3.3.1. Magnetic Resonance Imaging (MRI)

MRI uses the magnetic properties of tissue to produce an image. It stems from the application of nuclear magnetic resonance (NMR) to radiological imaging, namely the use of an assortment of magnetic fields to match the radio frequency of an oscillating magnetic field to the precessional frequency of the spin of some nucleus in a tissue molecule (Huettel, Song, & McCarthy, 2004). The source of the resonance in an NMR experiment is that the protons and neutrons that constitute a nucleus possess an intrinsic angular momentum called spin. Spin is a property of hydrogen atoms which creates a magnetic field (M) for each individual proton and M can be adjusted using magnets in the scanner.

The largest of the MRI magnets creates a static magnetic field (B0), when a participant is placed in the scanner M aligns with B0 and the protons remain in a low energy state. A

second magnetic field (B1) is produced by the radio frequency (RF) transmitter coil and acts as an external force which causes precession of M between the two magnetic fields. During precession the protons are in a high energy state, which causes M to flip and align with B1 until the RF transmitter is switched off when the protons begin to return to a low energy state and re-align with B0. Once the RF is switched off the three gradient coils are switched on introducing gradients in the strength of the magnetic field, these gradients in turn alter the rate of precession and help locate the origin of the MR signal in 3D space. The RF receiver coil records the MR signal emitted by protons as M realigns with B0 and protons return to low energy state, a process known as relaxation. The time it takes for a proton to realign with B0 and the extent of relaxation which occurs before the next RF pulse produces variation in the MR signal. Crucially, because protons in different tissue classes have different relaxation rates, recording the MR signal at different time points allows the identification of MR signal from specific tissue classes.

MR signal can be recorded from two types of relaxation process, which occur at different time points following cessation of B1. Spin-lattice (or longitudinal) relaxation reflects the time it takes for signal to increase in the direction of B0, specifically the time required for 63% of M to realign with B0. Spin-spin (or transverse) relaxation reflects the time it takes for signal to decay in the direction of B1, specifically the time required for 37% of M to decay back to its previous strength. Spin-lattice relaxation occurs early after B1 ends (known as time 1). Spin-spin relaxation occurs more slowly following cessation of B1 (at time 2). White matter produces the highest signal on T1 images, while CSF produces the highest signal on T2 images. These images are crucial for identifying structural abnormalities in clinical populations (particularly T2). The T1 image is crucial for neuroimaging investigations presented in this thesis, to allow localisation of function to underlying brain.

3.3.2. Functional Magnetic Resonance Imaging (fMRI)

Functional MRI works on similar principles as MRI, except it measures variation in the MR signal caused by the haemodynamic response of brain tissue to stimuli, as opposed to the relaxation of hydrogen atoms. Neural events in the brain are paralleled by a haemodynamic response which aims to meet the increased demand for glucose and oxygen from active neurons (Leniger-Follert & Hossmann, 1979). The co-occurrence of this haemodynamic response with neuronal activity is known as neurovascular coupling. The haemodynamic response reflects – in aggregate – changes in three aspects of cerebral dynamics; cerebral blood flow, blood volume and blood oxygenation (Ogawa, Lee, Kay, & Tank, 1990). The over-compensatory haemodynamic response increases the ratio of oxyhaemoglobin to deoxyhaemoglobin in the vasculature surrounding active neurons (Malonek & Grinvald, 1996). Because deoxyhaemoglobin is more strongly paramagnetic than oxyhaemoglobin, changes in the ratio of oxygenated and deoxygenated blood changes the local magnetic field strength. Local magnetic field inhomogeneities introduce variance in spin-spin relaxation times, which can be recorded at a specific time point (T2*) by the RF receiver coil. The variation in spin-spin relaxation caused by these local field inhomogeneities are the source of blood oxygenation level dependent (BOLD) signal. Essentially, we infer neuronal activity from this indirect measure of oxygen supply in the brain.

A change in BOLD signal caused by neural activity is known as haemodynamic response function (HRF). Statistical modelling used in the analysis of fMRI results assumes a similar haemodynamic response across individuals, regardless of cerebrovascular differences. The onset of the 'typical' haemodynamic response is delayed by ~2 seconds following stimulus

onset (Kwong et al., 1992). The increase in blood flow overcompensates for the increase in oxygen demand, resulting in an oversupply of oxygenated blood at its peak (Fox & Raichle, 1986; Fox, Raichle, Mintun, & Dence, 1988). The hemodynamic response function (HRF) reaches a plateau after 6-12 seconds, and then returns to baseline over a further 6-12 seconds. A post-stimulus undershoot is often evident (Frahm, Krager, Merboldt, & Kleinschmidt, 1996), see Fig 2. The shape of HDR varies with the stimulus properties and the underlying neuronal activity. Increasing the neuronal activity would therefore increase the HDR amplitude, whereas increasing the duration of neuronal activity would increase the HDR width. The change in BOLD signal is proportional to the underlying neural activity and will eventually plateau if the stimulus is sustained for a long period or return to baseline if the stimulus is removed. The signal intensity of each voxel collected during acquisition is then compared to a model of the expected BOLD response to the stimulus, and statistical tests are used to detect (small) significant signal changes which represent changes in neural activity.

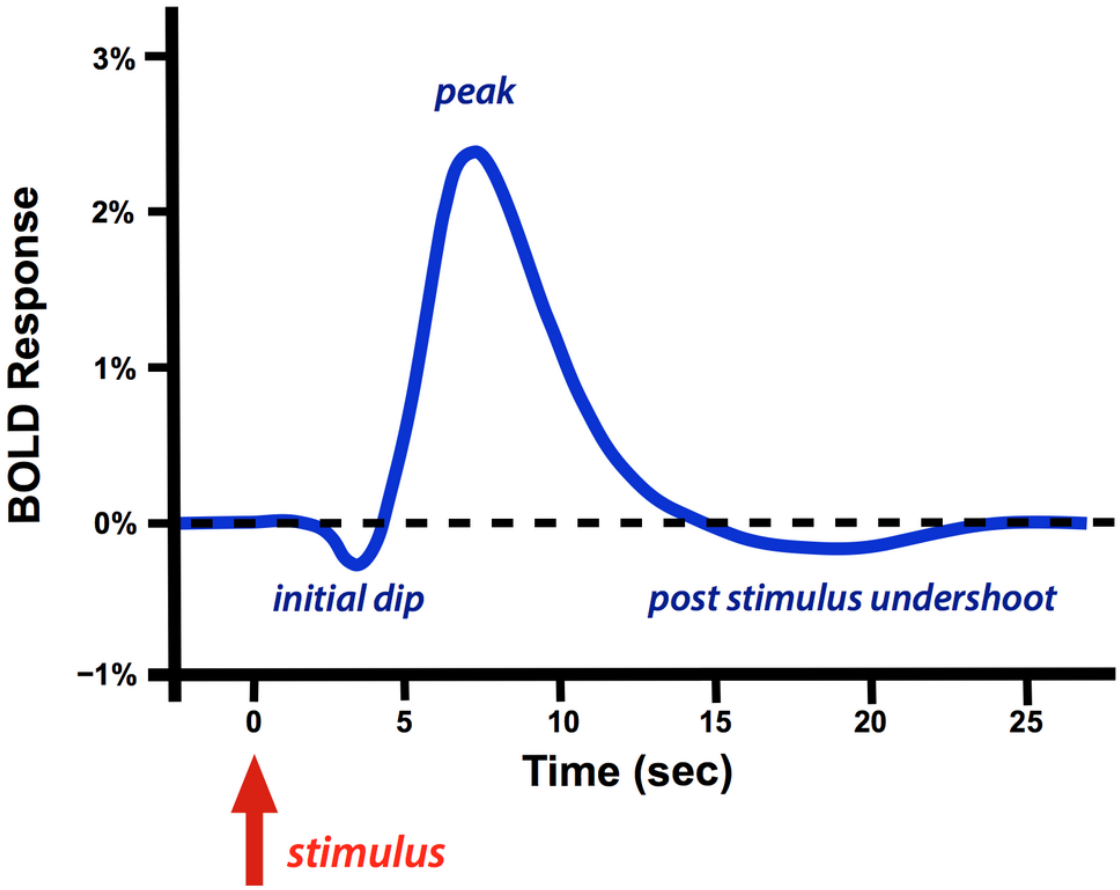

Fig 2. The dynamics of the haemodynamic response function.

Functional MRI studies are designed to induce different neural states using various stimuli which are then compared against each other, or against a 'control' condition e.g. fixation cross. The two main types of fMRI experimental design are the block design and event-related design. Using a block design, trials are arranged in 'blocks' and alternate between experimental and control conditions (e.g. ABACAB…) usually lasting around 20 seconds each. The data is then averaged across blocks for each participant and conditions are compared by 'subtracting' one from the other to identify brain regions representing performance of the task. This design has good power to detect voxel activation, localise functional areas and study steady-state processes. Alternatively, an event-related design presents stimuli briefly (a few

seconds) in non-constant intervals. This design is better for detecting transient changes in brain activity for each individual (e.g. errors) and preventing the participant from predicting stimulus presentations or habituating to the task. However, the design also lacks power because fewer events are averaged. Event-related design has been used in this thesis as tasks require that participants cannot predict stimulus presentation.

Conventional neuroimaging analysis methods have focused on characterising the relationship between cognitive tasks and brain regions; thus, they are known as univariate BOLD approaches. These methods look for clusters of neighbouring voxels that show a statistically significant response to the experimental conditions, and group analysis is typically performed after anatomical alignment of individual brains and enough spatial smoothing to overcome between-subject anatomical variability. Although the univariate approach reduces noise, it also reduces signal by neglecting the information carried by voxels with weaker (i.e. nonsignificant) responses to a particular condition. After pre-processing, the data can be analysed to localise brain activity, firstly at the individual subject level (first-level analysis) and then at the group level (second-level analysis). The most common first-level analysis method for modelling the activity in each voxel is the General Linear Model (GLM). This approach models the relationship between one or more explanatory variables and the response variable (BOLD signal) by fitting a linear equation to the observed data. At the group analysis stage, a mixed effect (or random effects) model is most commonly used to estimate the fixed effect β coefficient (i.e. the set of weights of predictors from the single-subject analysis) and the variance components between-subjects. These parameter estimates are then used in the statistical design to test whether there are significant activations on average across the sample in relation to the contrast of interest (i.e. high schizotypy vs low schizotypy) or if these are associated with a covariate (e.g. estimation errors). The statistical inference can be performed using parametric or non-parametric approaches. Voxel wise inference is a parametric approach

that treats each voxel independently and performs the statistical test at each individual level (i.e. testing whether each voxel intensity exceeds a threshold of significance). However, cluster-based statistics is a more robust approach to use as it considers the spatial extent of the voxel activation rather than just the peak height, by treating voxels as related. Clusters are first defined using a threshold and then cluster significance is tested by comparing the size of each cluster to a critical cluster size threshold. Both statistical approaches require correction for the multiple testing problem which occurs when multiple tests are performed, increasing the chance of false positives (especially in the case of fMRI when thousands of data points are being tested). Random Field Theory is commonly used to account for the multiple comparison problem by correcting the autocorrelated, 'smoothed' data to the family-wise error rate (corrected p-value of 0.05). RFT has been used consistently in the following neuroimaging chapters.

Permutation testing is a non-parametric approach to statistical inference. This approach is more commonly used now as a result of recent research that suggests conventional parametric methods (such as the voxel-wise and cluster-based approaches described above) are not robust because these tests assume that voxel activations are independent, that the underlying smoothness of the image is constant across the entire brain and that fMRI data is normally distributed which is generally incorrect (Eklund, Nichols, & Knutsson, 2016). Functional MRI studies also often suffer from small sample sizes and there may be concerns with assumptions of normality. Permutation testing does not assume the data are normally distributed. Instead, the method 'shuffles' the data (applying 10000 permutations as standard) to determine the exact distribution and then compares this to the observed data to test whether it is significantly different using a corrected p-value of 0.05. Threshold-free cluster enhancement is often used which allows cluster correction to be performed without requiring an arbitrary threshold. Permutation testing has been used for one of the three neuroimaging

chapters outlined in this thesis (the resting state analysis). The two fMRI chapters used parametric approaches following the analysis pipeline outlined in previous works with these tasks (Garrett et al., 2014; Kuzmanovic et al., 2015; Sharot et al., 2011; Sharot et al., 2012; Sevgi et al., 2020).

3.3.3. Resting State Functional Magnetic Resonance Imaging (rs-fMRI)

Resting-state fMRI (rs-fMRI) is a common FMRI method where BOLD data is acquired to evaluate functional connectivity while participants are at rest (not performing any specific task) and are given minimal instruction (e.g. keep your eyes closed). Rs-fMRI focuses on spontaneous, low frequency fluctuations in the BOLD signal (< 0.1 Hz). The observation that MRI could be used to monitor temporally correlated low-frequency activity fluctuations in spatially remote brain areas led to widespread use of rs-fMRI to evaluate resting state network (RSN) properties. These persistent, correlated spontaneous activity between brain regions (i.e. functional connectivity), initially thought to be noise (i.e., random error) in BOLD measurements, are in fact a meaningful source of information, reflecting a fundamental feature of brain functional organization (Raichle, 2009).

Several techniques have been developed to probe rs-fMRI data. In model-free approaches such as Independent Components Analysis (ICA), the spatio-temporal structure of the data is characterised into several independent components reflecting a functional network, physiological noise or image/acquisition artefact. However, defining the optimal number of components to be generated is arbitrary and varies from study to study which effects the number of patterns of connectivity that can be derived. Other analytical approaches include seed-based correlation analyses - where the time course from a ‘seed’ voxel (region of interest) is extracted and correlated with activity at each voxel (Van Den Heuvel, Martijn & Pol, 2010).

This approach allows for a much more straightforward interpretation of the data but limits the findings to networks that display connectivity only with the region of interest. Seed-based analysis was implemented in this thesis due to pre-defined hypothesis regarding particular regions.

3.3.4. Magnetic Resonance Imaging (MRS)

Proton magnetic resonance spectroscopy (MRS) is a non-invasive analytical technique associated with MRI imaging. Much like fMRI, MRS exploits the magnetic properties of atomic nuclei in the brain that possess spin such as hydrogen (1H-MRS). Instead of causing the spins to transition from an antiparallel to parallel state as with many fMRI sequences, spectroscopy sequences cause the spins to become polarised with the RF field and rotate along the static magnetic field (Lei, Xin, Gruetter, & Mlynárik, 2014). The hydrogen spins have small differences in frequency depending on the molecular structure the atomic nucleus is within and the chemical environment and geometric composition of the molecule, or 'J-coupling'. Specific nuclei contained within a metabolite therefore give rise to either a single peak or multiple peaks that are uniquely positioned along the frequency axis of the spectrum (Richards, 2001). This is also known as the 'chemical shift'. The relative concentrations of metabolites are then calculated from the areas under the spectrum peaks. These include aspartate, gamma-amino butyric acid (GABA), glucose, glutamate (Glu), glutamine (Gln), lactate, N-acetyl aspartate (NAA) and many more that have critical functions in the brain including neuroenergetics, neurotransmission, and neuromodulation. MRS therefore provides information about the biochemical composition of the brain as well as many pathophysiological processes including tumours (Gujar, Maheshwari, Björkman-Burtscher, & Sundgren, 2005).

The most common method of MRS is single voxel spectroscopy (SVS) which samples spectra from a single, predefined voxel (Bulakbasi, Kocaoglu, Örs, Tayfun, & Üçöz, 2003; Schubert, Gallinat, Seifert, & Rinneberg, 2004). In research, it is commonly used to probe the hydrogen nucleus (1H-MRS) whereas the carbon nucleus (13C-MRS) is often used clinically to assess disorders of brain metabolism. A voxel of interest, usually measuring 30 mm x 20 mm x 20 mm is placed in a pre-selected anatomical, functional or clinical target area of the brain in order to collect spectra from. MRS is not a very sensitive technique and so several procedures are performed to enhance the signal. MRS data is acquired by suppressing the water signal in the spectrum and by performing outer volume suppression around the outside of the volume of interest to minimise the signal from other brain regions. Shimming is also applied to ensure a homogeneous magnetic field needed to enhance the sensitivity and resolution of the acquired spectra by narrowing the peak width, increasing the SNR and improving water suppression. Furthermore, it is important to ensure the quality of the spectra is good and often spectra are excluded if they do not meet quality control criteria (usually Cramer-Rao Lower Bound (CRLB) < 20%). Within this thesis, MRS was used to measure metabolite levels from cortical brain regions using SVS.

3.3.5. Computational Modelling

Computational psychiatry is devoted to the development and application of mathematical models to psychiatric research and has had a significant impact on cognitive neuroscience (Stephan, Klaas & Mathys, 2014). The aim of the field is to construct abstract models based on integrated evidence from neuroscience and psychology in order to explain neural activity and cognitive behaviour. The first objective is to model the computations that

the brain performs (the brain's solutions to incoming problems) to thereby understand how the 'abnormal' perceptions, thoughts and behaviours defining psychiatric disorders relate to normal function and neural processes. By mathematically formalising the relationship between symptoms, environments and neurobiology, the field of computational psychiatry hopes to provide tools to identify the causes of symptoms in individual patients (Adams, Huys, & Roiser, 2016).

Many mathematical models exist that could address these aims, but Bayesian inference models have found a particularly widespread application to empirical behavioural and neuroimaging data. For example, the most popular explanations of brain message transfers are usually portrayed in the context of the Bayesian brain hypothesis as predictive coding, i.e. the brain constructs and continuously updates a generative model of the world (Clark, 2013; Diaconescu et al., 2017; Friston, 2008; Rao & Ballard, 1999; Srinivasan, Laughlin, & Dubs, 1982). There is now much circumstantial anatomical and psychological evidence to support the biological basis of this process theory within a Bayesian framework (Adams, Shipp, & Friston, 2013; Bastos et al., 2012; Diaconescu et al., 2017; Friston, 2008; Mumford, 1992; Shipp, Adams, & Friston, 2013; Vossel, Mathys, Stephan, & Friston, 2015). Within the Bayesian predictive coding process theory, neuronal representations in the higher levels of cortical structural hierarchies generate predictions of representations in lower levels. These top-down predictions are compared with representations at the lower level to form a prediction error, and this mismatch is passed back up the hierarchy to update higher representations. The uncertainty (inverse precision) at each level helps determine the learning rate at that level, that is, the size of the adjustments that are made to explain new data (Mathys, Daunizeau, Friston, & Stephan, 2011). In biological terms, prediction errors are associated with the activity of superficial pyramidal cells, whereas higher order representations are associated with the activity of deep pyramidal cells.

In computational terms, neuronal activity is thought to encode beliefs (i.e. probability distributions) over external states that cause sensations. However, the brain's sensory data and its prior knowledge are not completely reliable, and so the brain must use both sources of information—taking into account their uncertainty—to perform its task. The optimal combination of uncertain information is given by Bayes' theorem, in which a 'prior' (the initial expectation of the state of the environment) is combined with a 'likelihood' (the probability of the sensory input, given that expectation) to compute a 'posterior' (an updated estimation of the state of the environment). For simplicity, these probability distributions are often assumed to be of a kind that can be represented by a few 'sufficient statistics'; for instance, the mean and precision (inverse variance) of a normal distribution (Fig 3).

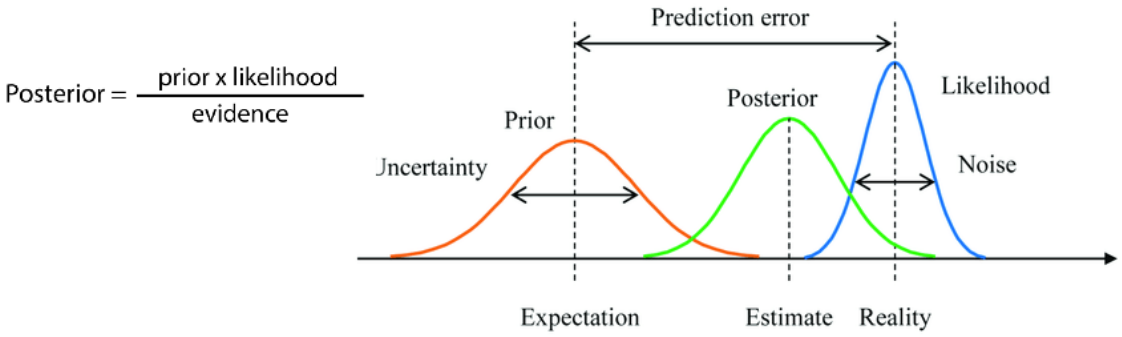

Fig 3. Example of Bayesian inference with a prior distribution, a posterior distribution, and a likelihood function. The prediction error is the difference between the prior expectation and the peak of the likelihood function (i.e. reality). Uncertainty is the variance of the prior. Noise is the variance of the likelihood function. Adapted from (Yanagisawa, Kawamata, & Ueda, 2019).

The simplest encoding associates the belief with the expected value of a (hidden) cause or expectation. These causes are referred to as hidden because they have to be inferred from their sensory consequences via precision estimates (inverse variance). For example, a smiling

face is the hidden cause of visual sensations that has to be inferred from the incoming visual input with a certain level of uncertainty. Thus, precision can be regarded as a measure of signal-to-noise, or the confidence, assigned to an information stream. Estimating precision is a fundamental aspect of inference in the brain and can be regarded as encoding the expected uncertainty in any given context (Angela & Dayan, 2005; Brown, Adams, Parees, Edwards, & Friston, 2013; Iglesias et al., 2013). This estimation represents a subtle but generic problem that the brain must solve, and the solution might rest on modulating the gain or excitability of neuronal populations that generate prediction error (Clark, 2013; Feldman & Friston, 2010; Friston, 2008). This key role of uncertainty in neural coding and neural computation has inspired several recent frameworks with considerable potential for advances in psychiatry research (Knill & Pouget, 2004). Furthermore, this predictive coding perspective has inspired concrete strategies for analysing empirical data.

One such framework with practical implications is the meta-Bayesian approach which considers the Bayesian inference (by an experimenter or psychiatrist) on Bayesian inference processes (in the brain of a subject or patient) that underlie the observed behavioural responses (Daunizeau, den Ouden, Pessiglione, Kiebel, Stephan, Friston, 2010). In other words, the analysis of behavioural responses made by subjects is itself based on perceptual inferences. The researchers thus have to make inferences about inferences (i.e. meta-inference) The basic problem tackled by meta-Bayesian approaches is to embed perceptual inference in a generative model of decision-making that enables us, as experimenters, to infer the probabilistic representation of sensory contingencies and outcomes used by subjects (as inferred by the subjects). In this framework one models how the subject's 'hidden' (internal) belief updating processes give rise to his/her overt responses which, in turn, are observed by the experimenter. The appeal of such a hierarchical approach is that the experimenter's beliefs (about the subjects' beliefs driving the observed behaviour) can be estimated by inverting a single

generative model and under the same assumption about how Bayesian inference is implemented in the brain (e.g., by free-energy minimization).

A key implementation of such a meta-Bayesian approach is the Hierarchical Gaussian Filter (HGF; Mathys et al., 2011). The HGF derives update equations (similar to learning models) from a variational approximation to ideal hierarchical Bayesian learning agent and contains parameters that represent the agent's approximation to Bayesian optimal learning (Fig 4). This framework has been used by several recent studies to adjudicate between competing hypotheses of learning and decision-making, using pathophysiologically relevant paradigms, such as perceptual learning (Iglesias et al., 2013) or cued eye movements (Vossel et al., 2014). It has also served as the basis for theoretical work on 'emotional valence' (in terms of the negative rate of change of free energy; (Joffily & Coricelli, 2013). Hierarchical Bayesian approaches are particularly useful for paradigms where uncertainty plays a crucial role, for example, induced by stimulus-bound (sensory noise) or environmental factors (volatility), and will be used in the current thesis to investigate social perception under uncertainty.

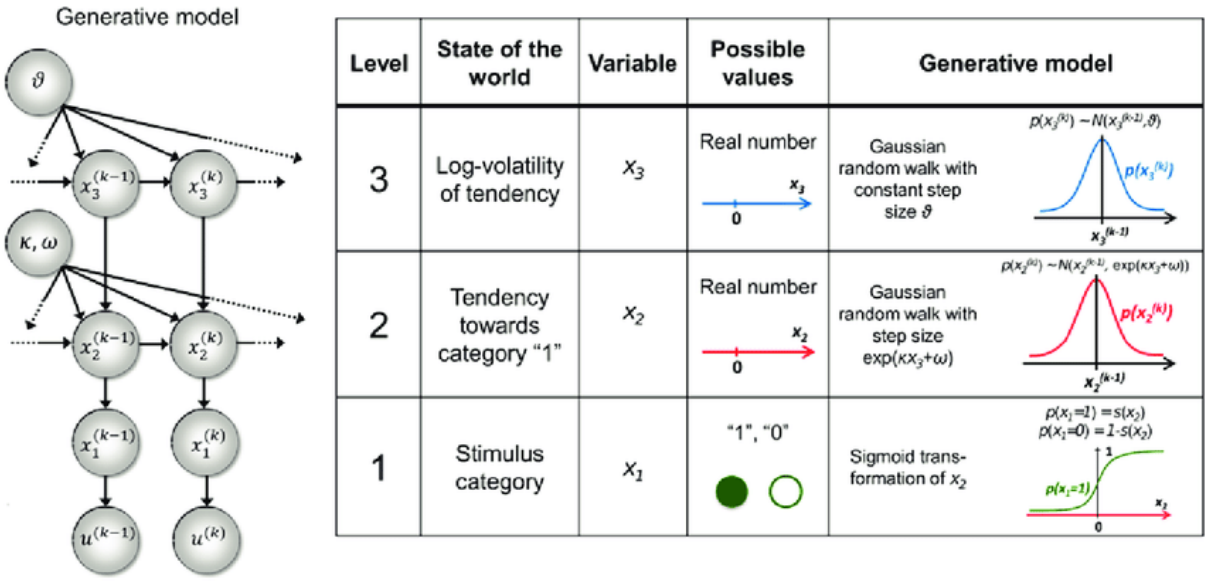

Fig 4. An overview of the hierarchical generative model, adapted from (Mathys, Daunizeau, Friston, & Stephan, 2011). The probability at each level is determined by the variables and parameters at the next highest level. These levels relate to each other by determining the step size (volatility or variance) of a random Gaussian walk (sufficiently described by its summary statistics).

The generative models implemented in the HFG describe how the observed data (i.e. brain activity; symptoms; behavioural responses) were generated by hidden mechanisms. A generative model defines a joint probability distribution p(y,θ) over observations (measured data y) and parameters θ. It has two components, a likelihood function p (y| θ) and a prior density of the parameters p(θ). It is called 'generative' because one can generate synthetic data by sampling parameter values from the prior and plugging these into the likelihood. One can thus also regard a generative model as a 'forward model' from parameters to observed data. 'Model inversion' refers to the opposite process: estimating the posterior probability of the parameters, given some observed data. Notably, by integrating out the dependency of the data on the parameters, one obtains the 'expected data', that is, the marginal likelihood or model evidence:

$$P(y) = \int p(y|\theta)p(\theta)d(\theta)$$

The model evidence is a principled measure for the generalizability of a model (i.e., its trade-off between accuracy and complexity of the model) and is widely used for model comparison with Bayesian model selection approaches (see Frank & Badre, 2012; Huys et al., 2012; Iglesias et al., 2013; Lieder, Daunizeau, Garrido, Friston, & Stephan, 2013; Payzan-LeNestour, Dunne, Bossaerts, & O'Doherty, 2013; Penny, 2012; Schmidt et al., 2013a; Schmidt et al., 2013b; Stephan, Penny, Daunizeau, & Friston, 2009; Vossel et al., 2014). Additionally, subjects may differ in the processes generating their behaviour, that is, the model itself may be a random variable in the population. This issue is particularly relevant for the heterogeneous spectrum disorders psychiatry deals with and has been addressed by the development of random effects BMS methods (Stephan et al., 2009). In summary, a generative model (as those utilised in the HGF) is a probabilistic description of how high-level causes actually generate low-level data, in contrast to discriminative models which describe how to label such data with their likely causes. In mathematical terms, discriminative models learn the probability of some causes given the data, whereas generative models learn the reverse: the probability of the data given some causes and use that probability (along with the probability of the causes and Bayes theorem) to compute the probability of the causes given the data.

This distinction is important because knowing how causes generate data allows a model to generate synthetic or 'simulated' data from given causes; i.e. we are modelling the brain's own model of the world (Adams, Aponte, Marshall, & Friston, 2015). By altering key parameters in our generative models of agents' brains, we can observe what effects they have on decision-making and use this information to optimise experimental design or make counter-intuitive predictions. Bayesian statistics and machine learning techniques then allow this entire description to be tested against real data for goodness-of-fit. Comparisons of generative models by means of Bayesian model selection offer among the most rigorous and global comparative assessment of scientific hypotheses (Stephan et al., 2009). Furthermore, computational

generative models are well suited to address differential diagnosis, that is, to infer, from observed behaviour and brain physiology, on the most likely disease mechanism in a patient. In other domains of medicine, such differential diagnosis is often supported by (biochemical) assays which allow for inference on 'hidden' disease mechanisms from peripherally accessible tissue (e.g., blood). An attractive idea is to use computational models for establishing equivalent procedures in psychiatry, using non-invasive functional read-outs instead of tissue samples. These 'computational assays' have been suggested in the form of generative models that can be fitted to measurements of brain activity and behaviour (Stephan, Baldeweg, & Friston, 2006) as done in the current thesis.

The majority of existing computational treatments of psychiatric diseases concern aberrant learning and decision-making as core components of maladaptive cognition. With particular focus on schizophrenia, this computational perspective has provided theoretical frameworks of (mal)adaptive cognition with a specific focus on abnormal beliefs (Adams, Perrinet, Friston, 2012; Corlett, Taylor, Wang, Fletcher, & Krystal, 2010; Fletcher & Frith, 2009; Stephan et al., 2006). A recurrent theme in many psychiatric disorders is a failure of sensory attenuation, with secondary consequences for the acquisition and deployment of hierarchically deep models of the world, and interpersonal interactions. In the context of sensory exchanges with the world, such as pursuit eye movements, a failure of sensory attenuation means that sensory precision is too high in relation to the precision of higher (prior) beliefs about the causes of sensations. It is relatively easy to reproduce the key deficits of slow pursuit eye movements in schizophrenia by simply reducing prior precision in simulations of eye tracking using predictive coding and oculomotor reflexes (Adams et al., 2012). This mechanism might explain the inability of patients with schizophrenia to infer regular (high order) contingencies that underlie target movement and anticipate its motion. Because prior

expectations are compromised in schizophrenia, violations (e.g., unpredicted changes in target motion) paradoxically improve pursuit performance, relative to people without schizophrenia.

Simulation of delusional beliefs is also straightforward within a hierarchical Bayesian inference schemes such as predictive coding, because these models deal explicitly with expectations. Perhaps the best example addresses beliefs about agency—a key issue in schizophrenia research. Some patients with psychiatric disorders fail to contextualise the consequences of their actions and make false inferences about the agency or authors of their sensory outcomes. This is demonstrated nicely by the resistance of patients with schizophrenia to the force-matching illusion (Shergill, Samson, Bays, Frith, & Wolpert, 2005; Shergill et al., 2014). Normally, people show sensory attenuation when they do something, whereas patients with schizophrenia seem not to. The force-matching illusion reduces the perceived magnitude of self-produced forces relative to externally generated forces. Crucially, patients with schizophrenia are resistant to this illusion and can accurately report the forces that they produce themselves (Shergill et al., 2005). This result can be simulated in predictive coding of somatosensory and proprioceptive cues by, precluding an attenuation of sensory precision (Brown, Adams, Parees, Edwards, & Friston, 2013). However, this comes at a price—to produce the self-generated force in the first place, non-sensory (or prior) precision must be increased so that an individual's prior belief that they are moving over-rides the sensory evidence that they are not. The problem here is that to explain the precise sensory information (that the force is always less than predicted) the person has to infer an opposing external force. This scenario is a good example of a simulated delusional belief that rests on one simple manipulation, a failure to attenuate sensory precision and compensatory increases in precision at higher levels of the hierarchy (Friston, Stephan, Montague, & Dolan, 2014).

Computational analyses have also provided a mechanistic explanation for cognitive biases in schizophrenia, such as the jumping to conclusions bias or the disconfirmatory evidence bias implicated in models of delusion formation. Computational approaches with the HGF have shown that subjects with a diagnosis of schizophrenia make large adjustments to their beliefs following unexpected evidence, but also smaller adjustments than controls following consistent evidence (Adams, Napier, Roiser, Mathys, & Gilleen, 2018). A mechanistic explanation of these cognitive biases and computational results may be that in schizophrenia patients neural firing patters are less stable and hence easily altered in response to both new evidence and stochastic neural firing (Hamm, Peterka, Gogos, & Yuste, 2017; Rolls, Loh, Deco, & Winterer, 2008). In other words, the observed cognitive biases can be explained by both overweighting unexpected evidence and underweighting consistent evidence driven by vulnerability to stochastic fluctuations in neural activity. To provide a mechanistic explanation of social cognition biases in schizotypy samples and to account for the link of these mechanisms with neural activity, we employed HFG for the analysis of the social perception inference task in this thesis.

3.4. General Methods

3.4.1. Participants

1342 participants responded to an online survey advertised via social media and were pre-screened using the Schizotypy Personality Questionnaire (SPQ; Raine, 1991) and the Marlowe-Crowne Social Desirability Scale (SDS; Fischer & Fick, 1993). All participants that took part in the MRI study were recruited from the student population of the Royal Holloway University of London. Exclusion criteria was defined as: presence of contraindicators for MRI

scanning (presence of metal, etc.), current use of prescribed medication for neuropsychiatric disorders or history of neuropsychiatric disorders, current use or history of illicit substances misuse. These criteria were assessed via self-report and pre-screening for MRI scanning. Furthermore, the SDS questionnaire was used to exclude participants that give mainly socially desirable answers (Fischer & Fick, 1993). The SDS questionnaire includes items that describe culturally approved behaviours that are improbable to occur, thus higher scores indicate participants are likely to distort their responses by providing the desirable rather than the likely answer. To limit this type of distortion in our self-report data, we only included participants who do not present with socially desirable response bias. Thus, subjects who scored 8 or higher on the SDS (out of 13, as utilised by previous research; Fischer & Fick, 1993) were excluded from the study due to giving mainly socially desirable answers (Loo & Thorpe, 2000).

Subjects were invited to take part in the study based on their SPQ score. The SPQ questionnaire which provides an overall measure of individual differences in schizotypal personality traits and can be reduced to three latent dimensions (positive, disorganised and negative; Vollema, Sitskoorn, Appels, & Kahn, 2002) mimicking the symptom clusters of schizophrenia and clinical high-risk states. Meehl assumed that only about 10% of individuals with schizotypy traits will transition to psychosis (Meehl, 1990). People with high schizotypy have an elevated risk of developing psychosis compared to the general population, with studies estimating that around 2% of high schizotypy individuals meet criteria for a schizophrenia-spectrum diagnosis at a 10-year follow-up assessment (Kwapil, Gross, Silvia, & Barrantes-Vidal, 2013; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). Crucially, the SPQ has been shown to be related to clinical diagnosis of schizotypal personality disorder. Raine (1991) found that 55% of those who scored in the top 10% of total SPQ score in a large sample qualified for diagnosis of schizotypal personality disorder. The aim of the thesis was to be informative of risk to progression to psychosis, thus we only recruited the bottom and top

10% decilles of the schizotypy continuum. This meant individuals scoring below 12 and above 41 points on the SPQ were invited to take part in the study (as informed by previous research; Raine, 1991; Raine et al., 1994).

This also ensures individuals will be scoring high on all subfactors of the SPQ as well. A number of investigations of schizotypy samples suggest that rating of schizotypal dimensions significantly relate to later development of either psychotic disorders or schizophrenia spectrum disorders (Bogren et al., 2010; Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994; Gooding, Tallent, & Matts, 2005; Kwapil, 1998; Kwapil et al., 2013; Miettunen et al., 2011; Salokangas et al., 2013). More specifically, these investigations suggest that the positive subfactor is mainly associated to the later emergence of psychotic disorders, while the negative subfactor (especially anhedonia) is rather selectively associated with the emergence of nonpsychotic schizophrenic-spectrum disorders. Salokangas and colleagues reported that schizotypal features indicate proneness to psychosis in the general population with their analysis of the European Prediction of Psychosis Study (Salokangas et al., 2013). In clinical-high risk individuals, self-reported baseline SPQ scores (specifically ideas of reference and lack of close interpersonal relationships subfactors) were associated with the 7% increased risk of transitions to psychosis (Salokangas et al., 2013). The co-occurrence of these schizotypy traits doubled the risk of transition at 18 months follow-up (risk at 26%), and this risk remained significant after controlling for a schizophrenia-spectrum diagnosis (Salokangas et al., 2013). Furthermore, significant preliminary longitudinal data on developing schizotypy support the importance of assessing schizotypy in its multifactorial nature. At least 3 reports suggest that during adolescent development, crucial interactions between positive, negative and disorganized schizotypy take place to both sustain/exacerbate schizotypal expression, and augment the risk for significant psychotic outbreaks (Debbané, Badoud, Balanzin, & Eliez, 2013; Dominguez, Saka, Lieb, Wittchen, & van Os, 2010; Kwapil et al., 2013). These

investigations support our approach of utilising total high schizotypy score, rather than any individual dimension, as multidimensional assessments of schizotypy enable a differential risk assessment for schizophrenia clinical disorders.

The final sample included 27 participants in the high schizotypy group (HS; 17 females, age range 18-22, M = 19.25, SD = 1.05) and 26 participants in the low schizotypy group (LS; 19 females, age range 18-27, M = 20.38, SD = 2.02). Each subsequent chapter in this study utilises a slightly different subset of this final sample, due to participant exclusion based on motion correction for neuroimaging analysis or quality control issues. As such sample characterises are reported in each chapter separately. Thus, we employed non-probability voluntary sampling to recruit individuals to complete the online survey. Then the final sample was selected from this using stratified (strata being high and low schizotypy) random probability sampling to allow us to make inferences at the population level.

Ethical approval for the study was obtained from the University of Roehampton's Ethics Committee and all participants provided informed written consent before initiating any study procedures. Participants were compensated for their time (£40 cash payment and a high-resolution anatomical scan of their brain). Ethical procedures complied with the Declaration of Helsinki regarding human experimentation.

Chapter Four

High schizotypy traits are associated with increased frontal cortex activity in response to estimation errors tracking social belief updating

Abstract

Schizophrenia patients present with numerous abnormalities in social cognition, including impaired emotional processing and inferring the intentions of others. Moreover, these deficits predict clinical outcome and relapse. Previous schizotypy investigations suggest that the high end of the continuum also presents with abnormal neural response during social cognition tasks albeit in the absence of behavioural deficits. Yet, previous work in high schizotypy groups has not investigated the way beliefs are updated in reference to social vs non-social information, or what neural networks may respond to social prediction errors in schizotypy samples. To this end, we used a belief-updating task to investigate the way high (n= 23) and low (n=24) schizotypy participants update their beliefs in response to social vs non-social information during functional Magnetic Resonance Imaging (fMRI). There were no behavioural group differences in task performance, yet the sample as a whole updated their beliefs more in response to social information (as compared to non-social information). fMRI results indicate that social positive and social negative estimation errors were associated with greater activity in the ventromedial prefrontal cortex and left inferior frontal gyrus, and lower activity in the dorsolateral prefrontal cortex in high relative to the low schizotypy subjects. This suggests that socially salient prediction errors require greater ventral prefrontal activity in high people with high levels of schizotypy during belief updating. However, in response to individual task conditions, the high schizotypy subjects presented with lower activity in frontal

cortex and ventral striatum in response to tracking prediction errors. These results suggest high schizotypy traits are associated with abnormal neural responses to prediction errors and draw a parallel with schizophrenia samples.

4.1. Introduction

People with high schizotypy (HS) have an elevated risk of developing psychosis compared to the general population, with studies estimating that around 2% of these individuals meet criteria for a schizophrenia-spectrum diagnosis at a 10-year follow-up (Kwapil et al., 2013; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). Thus, investigating schizotypal traits in non-clinical samples may provide important information about aetiological mechanisms underlying risk for psychosis, without the presence of clinically common confounders (i.e. medication, comorbidity). A better understanding of neurobiological mechanisms may provide useful knowledge that helps us to develop early detection strategies, biomarkers and preventive interventions for those at risk of psychosis (Barrantes-Vidal, Grant, & Kwapil, 2015).

The behavioural profiles associated with high schizotypy traits are qualitatively similar, but less severe than the symptoms found in patients with a schizophrenia-spectrum diagnosis. Namely, studies have reported that similar to patients with schizophrenia, HS individuals show deficits in cognition and perception (Ettinger, Meyhofer, Steffens, Wagner, & Koutsouleris, 2014) and in emotional/social cognition (Phillips & Seidman, 2008), albeit at a less severe level than patients with schizophrenia,

In particular, social cognition deficits, are a crucial area for research in these populations, because poor social functioning is linked to a lower quality of life (Penn, Corrigan,

Bentall, Racenstein, & Newman, 1997) and predicts illness outcome in schizophrenia, including relapse, poor illness course and unemployment (Álvarez-Jiménez et al., 2012; Brune, Schaub, Juckel, & Langdon, 2011; Couture, Penn, & Roberts, 2006; Kring & Elis, 2013). Individuals with schizophrenia often display marked impairments in processing social information, which can result in misinterpretations of the social intent of others, social withdrawal and impaired daily social functioning (Fett et al., 2011; Green, Hellemann, Horan, Lee, & Wynn, 2012). Indeed, in such individuals, social cognitive impairment has a more negative effect on daily functioning than does non-social cognitive impairment (Fett et al., 2011; Green et al., 2012).

Social cognition refers to the psychological processes that are involved in the perception, encoding, storage, retrieval and regulation of information about other people and ourselves (Adolphs, 2009; Brothers, 1990). These processes include social cue perception, experience sharing, inferring other people's thoughts and emotions, and managing emotional reactions to others. Patients with schizophrenia show widespread impairment in the processing of social information, particularly when processing emotional stimuli and when inferring the intentions of others (Green, Horan, & Lee, 2015; Penn, Sanna, & Roberts, 2008; Pinkham, 2014; Sprong, Schothorst, Vos, Hox, & Van Engeland, 2007; Ventura, Wood, Jimenez, & Hellemann, 2013). Crucially, social cognitive deficits are evident early in the course of the disorder and are stable over time (Frith, 2014; Green et al., 2015; Horan et al., 2011; Pinkham et al., 2005; Pinkham et al., 2007). Early identification of individuals who are at either clinical or genetic risk for developing schizophrenia shows that these impairments are present in high risk and prodromal phase of the illness (Addington, Penn, Woods, Addington, & Perkins, 2008; Chung, Kang, Shin, Yoo, & Kwon, 2008; Phillips & Seidman, 2008). A recent review of the neural correlates of populations at varying levels of risk for developing schizophrenia reported that prefrontal regions reliably showed differential activations in at-risk groups during

social cognition tasks (Kozhuharova, Saviola, Ettinger, & Allen, 2020). The mPFC, ventromedial PFC (vmPFC), inferior frontal gyrus (IFG) and superior frontal gyrus (SFG) show both increased and decreased patterns of activation in both schizotypy populations (Healey, Morgan, Musselman, Olino, & Forbes, 2014; Modinos, Renken, Shamay-Tsoory, Ormel, & Aleman, 2010; Modinos, Ormel, & Aleman, 2010; Modinos, Renken, Ormel, & Aleman, 2011; Mohanty et al., 2005; Wang et al., 2018) and in populations at clinical high risk for schizophrenia (Modinos et al., 2015a; Modinos et al., 2015b; Pelletier-Baldelli, Orr, Bernard, & Mittal, 2018; Seiferth et al., 2008; Stanfield et al., 2017; Wolf et al., 2015). Neuroimaging studies have implicated regions in the PFC in inferring the internal states and intentions of others, in regulating emotion, in processing reward and punishment and in the contextual interpretation of complex social information (Phan, Wager, Taylor, & Liberzon, 2002). The consistent patterns of altered activity in these regions in at-risk populations during social cognition tasks might represent abnormal processing of socially salient cues leading to aberrant beliefs about others and thus contributing to the formation of delusions (Corlett, Taylor, Wang, Fletcher, & Krystal, 2010; Morrison, Renton, Dunn, Williams, & Bentall, 2004). Considering that social cognition deficits are predictive for future onset of schizophrenia-spectrum disorders in psychosis risk populations (Kwapil, 1998), specifying the nature and extent of these deficits, and the corresponding neural abnormalities, in different psychosis risk populations may help built a comprehensive model of the progression of this potential endophenotype during illness prodrome.

Despite a number of previous studies reporting social cognitive deficits measured with tasks measure emotion processing (Edwards, Jackson, & Pattison, 2002; Kohler & Brennan, 2004; van't Wout, Aleman, Kessels, Cahn, de Haan, & Kahn, 2007); ToM (Corcoran, Mercer, & Frith, 1995; Greig, Bryson, & Bell, 2004), social perceptions and judgements (Baas, van't Wout, Aleman, & Kahn, 2008; Corrigan & Green, 1993; Toomey, Schuldberg, Corrigan, &

Green, 2002) and social knowledge or understanding social schema (Corrigan, Patrick & Addis, 1995; Penn, Ritchie, Francis, Combs, & Martin, 2002), currently very little is known about the mechanisms driving learning from socially salient cues. To this end, we employed a modified version of a well-validated belief updating task to allow us to measure the neural correlates associated with socially salient (vs non-social) prediction errors in at-risk populations.

The paradigm assessed how people update their initial beliefs about risks of experiencing hazards (Garrett & Sharot, 2017; Korn, Sharot, Walter, Heekeren, & Dolan, 2014; Moutsiana, Charpentier, Garrett, Cohen, & Sharot, 2015; Sharot, Guitart-Masip, Korn, Chowdhury, & Dolan, 2012). Participants first estimate the probability that an adverse event would occur in the future and are then presented with the official base rate of this event occurring in the general population. Thereafter, participants are given the chance to revise their initial estimate (Kuzmanovic, Jefferson, & Vogeley, 2016; Kuzmanovic & Rigoux, 2017; Kuzmanovic, Rigoux, & Vogeley, 2019). Measuring learning in this task follows the computation of estimation errors (i.e. the difference between one's initial estimate and the base rate) and can be assumed to follow formal learning models, where the amount of learning depends on the size of the experienced prediction error (Pearce & Hall, 1980; Sutton & Barto, 2011). Numerous previous studies utilising these paradigms have shown that updating beliefs is optimistically biased because it was larger after desirable new information (lower risk that initially expected) than after undesirable information (higher risk that initially expected (Sharot, Korn, & Dolan, 2011; Sharot et al., 2012; Sharot & Garrett, 2016). For example, highlighting previously unknown risk factors for diseases is surprisingly ineffective at altering an individual's optimistic perception of their medical vulnerability (Gerrard, Gibbons, & Reis-Bergan, 1999; Weinstein & Klein, 1995). Although the extent of this optimism bias in belief updating can considerably differ across individuals depending on age, trait optimism,

depression, and reduced neural tracking of estimation errors (Chowdhury, Sharot, Wolfe, Düzel, & Dolan, 2014; Garrett et al., 2014; Korn et al., 2014; Kuzmanovic, Jefferson, & Vogeley, 2015; Kuzmanovic et al., 2016; Sharot et al., 2011), the effect was significant at the group level in all the mentioned studies (for healthy participants). Here we set out to investigate if this aversion to incorporating new information for undesirable news is also present in in people with high levels of schizotypy. Crucially, we compared judgements referring to social events with those about non-social events to investigate if schizotypy traits affect the way participants update their beliefs when the event is socially salient, i.e. whether learning varies with changes in the social nature of the events. To this end, we investigated the neural substrates that track prediction errors in response to both differentially valence-charged events and social/non-social events in high vs low schizotypy individuals.

Previous studies have consistently identified the frontal cortex and regions in the limbic cortex that support belief updating (Garrett et al., 2014; Garrett & Sharot, 2017; Kuzmanovic et al., 2016; Moutsiana et al., 2015; Sharot et al., 2012; Sharot & Garrett, 2016). Imprecise weighting of negative estimation errors is related to a relative failure to encode them in frontal brain regions, particularly the inferior frontal gyrus (IFG) and medial frontal cortex (MFC), compared to adequate coding of positive estimation errors (Sharot et al., 2011). Across individuals, the asymmetry in neural representation of estimation errors is predictive of subsequent failure to alter beliefs in response to undesirable information (Sharot et al., 2011). There is also an interaction between these frontal regions and the amygdala, striatum, thalamus, and insula (which all play a role in emotion, valuation, and motivation) that underlies asymmetric learning (Moutsiana et al., 2015). This is characterized both by an increased tendency to alter beliefs in response to desirable information and a reduced tendency to alter beliefs in response to undesirable information (Moutsiana et al., 2015). The IFG is involved in error-monitoring (Cools, Clark, Owen, & Robbins, 2002), risk prediction-error (d'Acremont,

Lu, Li, Van der Linden, & Bechara, 2009) and inhibition (Aron, Robbins, & Poldrack, 2004). The mPFC is suggested to represent the positive subjective value of rewards and emotional stimuli (Chase, Kumar, Eickhoff, & Dombrovski, 2015; Levy & Glimcher, 2012). Crucially, research in schizotypy and schizophrenia samples has reliably shown that these frontal cortex areas are abnormally activated during a range of tasks in these groups (Anticevic & Corlett, 2012; Anticevic et al., 2010; Kozhuharova et al., 2020; Takahashi et al., 2004; Taylor et al., 2002; Whalley et al., 2009). As explained earlier, these regions are also relevant for higher level social cognition such as inferring the beliefs of others (Adolphs, 2009; Ochsner, 2008). The midbrain regions linked to asymmetric learning in belief updating tasks (i.e. thalamus, insula, striatum) have also been reported as impaired in schizophrenia samples and have been linked to the widespread emotion processing deficits observed in these samples (Hall et al., 2008; Holt et al., 2006; Surguladze et al., 2006). Thus, we speculate that the abnormal functioning of these regions could also translate into abnormal learning from errors in response to social vs non-social cues and could affect the level of learning in social context.

Here we utilise the belief updating task in combination with fMRI to examine whether schizotypy traits are associated with neural responses that are likely to support a more biased integration of information about social future events. We hypothesise that, behaviourally, we will replicate previous studies and report an optimism bias across the sample (Garrett & Sharot, 2017; Sharot et al., 2011; Sharot et al., 2012). We expect to find more updating in social vs non-social conditions, in line with previous research indicating that social information is of particular importance for people over and above non-social information (Adolphs, 2001; Adolphs, 2003a; Adolphs, 2003b; Adolphs, 2009). We predict that there will be no behavioural differences between high and low schizotypy individuals in terms of behavioural responses to the task (i.e. updating) due as reported in previous reviews (Kozhuharova et al., 2020). We predict, whilst behavioural performance is unaltered, HS individuals will show abnormal

prefrontal cortex activity in response to social prediction errors. Because previous work has shown that high schizotypy traits are associated with increased activity in the prefrontal cortex, compared to healthy controls, in response to social tasks (Kozhuharova et al., 2020; Modinos et al., 2010b; Modinos et al., 2011; Mohanty et al., 2005) and with altered activity in a fronto-striatal network responding to prediction errors (Corlett & Fletcher, 2012), we hypothesis that relative to LS participants, HS participants will show increased activity in prefrontal and striatal regions during social belief updating.

4.2. Methods

4.2.1. Participants

Data collection and participant sampling strategies are described in the General Methods subsection of the third chapter. The final sample included 27 participants in the high schizotypy group (HS; 17 females, age range 18-22, M = 19.25, SD = 1.05) and 26 participants in the low schizotypy group (LS; 19 females, age range 18-27, M = 20.38, SD = 2.02).

Ethical approval for the study was obtained from the University of Roehampton's Ethics Committee and all participants provided informed written consent before initiating any study procedures. Participants were compensated for their time (£40 cash payment and a high-resolution anatomical scan of their brain).

4.2.2. Behavioural assessments

On the day of MRI scanning participants completed a validated short version of the Wechsler abbreviated scale of intelligence (WASI II; McCrimmon & Smith, 2013) to assess

intellectual ability. Working memory was assessed using the digit span backward task (Dobbs & Rule, 1989). Analysis of demographic and questionnaire data with the effect of group being tested using chi square test or independent samples t-test for parametric data (significance threshold $p < .05$) was performed.

4.2.3. Stimulus Material

We used 60 short descriptions of adverse life events as stimuli (list compiled from previous work; (Kuzmanovic et al., 2015; Kuzmanovic et al., 2016; Sharot et al., 2011; Sharot et al., 2012). The assignment of the stimuli to the valence experimental conditions (desirable vs undesirable news) and the order of trials were randomized anew for each participant. Trials were split into social vs non-social events by assessing if they involve an action by/with another person. Examples of social events: victim of bullying, bicycle theft, get teased/made fun of, get lied to, being cheated on. Examples of non-social events: getting a migraine, high blood pressure, severe insomnia; hearing problems; losing a valuable possession. The research team agreed by consensus on the type of every event (i.e. social vs non-social), if there were disagreements between research investigators the respective events were not included. Note that by applying a random assignment of the stimuli to each experimental conditions, event characteristics that have been suggested to modulate the optimism bias (e.g. base rate, arousal, event valence, controllability, personal experience; Cultural differences in unrealistic optimism and pessimism: the role of egocentrism and direct versus indirect comparison measures; neural mechanisms mediating optimism bias; unrealistic optimism about future life events; unrealistic optimism about susceptibility to health-problems-conclusions from a community wide sample) or general stimulus characteristics (e.g. number of letters or words) were equally distributed

across the experimental conditions and thus do not constitute confounding variables (see also Kuzmanovic et al., 2015).

4.2.4. Design and procedure

In each trial of the belief updating task, participants first had to estimate the probability that different adverse events would occur at least once in a lifetime. Next, they were presented with a corresponding base rate for the general population and were then given the opportunity to adjust their initial estimate (see Fig 1. for illustration and durations of events). The intervals within the trials and between the trials randomly varied, with a jitter of 2s and 3s respectively (see Fig 1). The successive arrangement of i) the first estimate, ii) the presentation of the base rate and iii) the second estimation within one trial served the purpose of minimizing confounding memory effects (Kuzmanovic et al., 2015; Kuzmanovic et al., 2016).

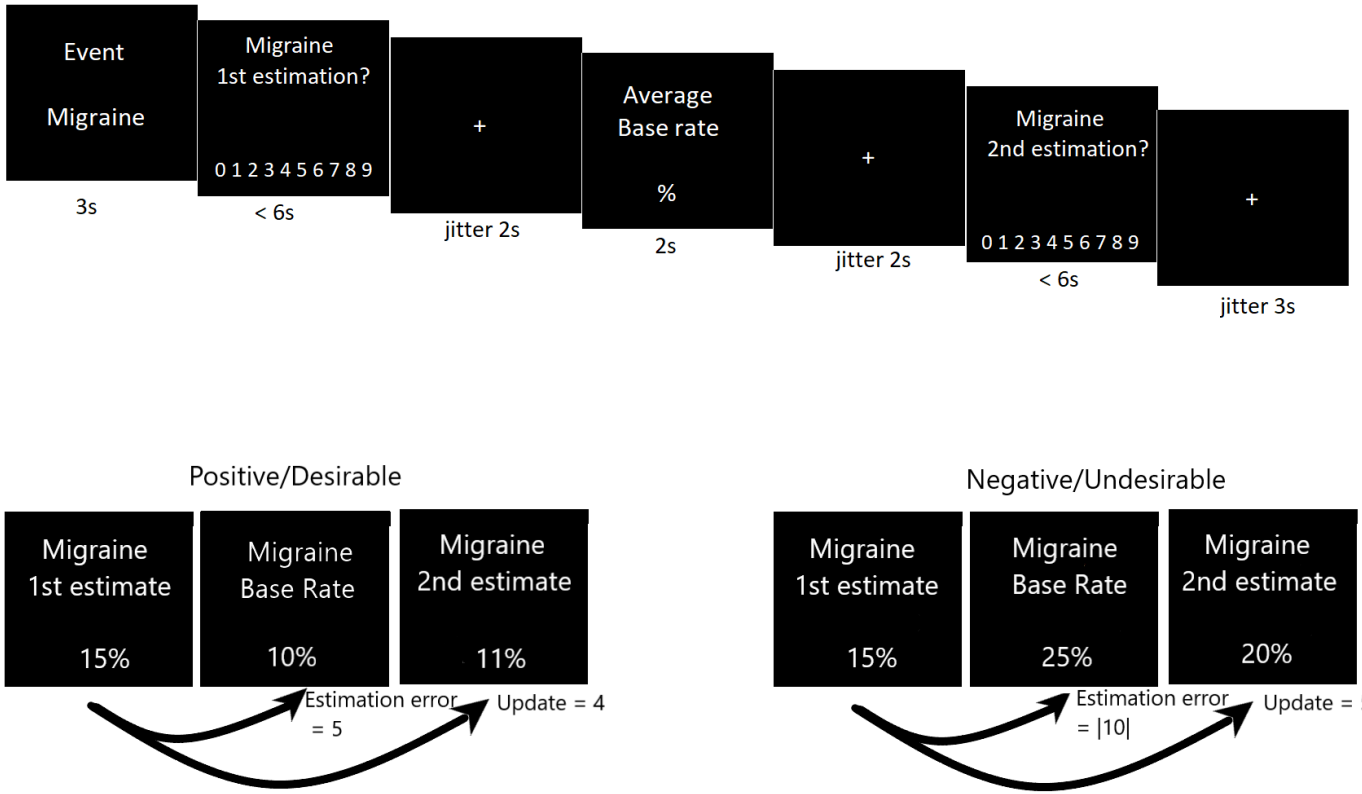

Fig 1. Example trials of the update experiment. At the beginning of each trial, participants were presented with the adverse event. Then participants were asked to estimate the probability of experiencing this event at least once in their lifetime. Then, the base rate of the respective event in the general population was presented. Finally, participants had the opportunity to update their initial estimate. Unbeknownst to participants, the valence of the presented base rate was experimentally manipulated by subtracting varying values from participant's first estimate. Second row left panel: An example of a positive trial, where the presented base rate is lower than the initial estimate (i.e. chance of adverse event happening is lower than initially assumed). Second row, right panel: An example of a negative trial, where the presented base rate is higher than the initial estimate (i.e. chance of adverse event happening.

The factors that were expected to affect updating behaviour within the task (i.e. independent variables) were the type of event (social, non-social), the valence of the new information (desirable, undesirable) and participants' schizotypy group (high, low). The dependent variables were Estimation Errors and size of updates.

Participants were not told that half of the events will be social in nature (s) or non-social (ns) to avoid biasing responses. The valence of the new information referring to the base rates of adverse events depended on participant's initial rating in each trial: When the base rate for an adverse event was lower than participants' first estimate, then this constituted desirable or positive (p) information; when it was higher than the first estimate, then this constituted undesirable or negative information (n). Thus, a 2x2x2 mixed design was appropriate with the factors type (social vs non-social) and valence (p vs. n), resulting in four within-subject conditions/interaction terms s_p, s_n, ns_p, ns_n, and the between-subject factor schizotypy group (high vs low).

Participants were told that the experiment aims to investigate the neural substrates of expectations towards future life events, as in previous studies with this task (Kuzmanovic et al., 2015; Sharot et al., 2011). They were instructed that there was no right or wrong answer as we were interested in their subjective judgement, and to feel free to update their estimate as much as they wanted. They were also informed that the population base rates were determined by the UK.gov or National Health Service official statistics, and that they should consider this information during their second estimation.

Unbeknownst to participants, the base rates were in fact systematically manipulated in order to control for frequencies and distributions of desirable and undesirable trials so that half of the trials were desirable and half undesirable (Kuzmanovic et al., 2015; Kuzmanovic et al., 2016). Desirable and undesirable base rates were computed by subtracting or adding varying

values form the first estimate (ranging from 1 to 25, Kuzmanovic et al., 2015; Kuzmanovic et al., 2016). In a final debriefing, participants were informed that they had been deceived about the source of population base rates, and the methodological reasons for this procedure were explained.

Participants were instructed to give responses by selecting an absolute probability number with a possible range from 1% to 99% (i.e. the probability of this event occurring at least once in a lifetime). Participants always used both hands and were given 10 buttons to choose from to select a respective number, participants could see the numbers on the screen throughout the task in the same order as the buttons they were using. Participants were told to always provide a 2-digit response (choosing the 0 first for responses where the probability was less than 10%), once a button was pressed the colour of the respective number on the screen would change so participants know the response is recorded. Participants were instructed to answer within 6 seconds. If a response was not recorded within this time, the rest of the trial was omitted. Durations of the two task sessions were 12 minutes each (30 events in each session).

After the fMRI acquisition, participants completed a short debriefing including the opportunity to describe problems or hypotheses regarding the purpose of the task. Importantly, because we manipulated the base rates, we took great care to assess participants' suspicions regarding their plausibility by using the funnel debriefing method used in previous studies (Kuzmanovic et al., 2015). Prior to the fMRI experiment, participants underwent a standardized, computerized instruction including practice trials with stimuli not used within the experimental tasks.

4.2.5. Behavioural analysis

Behavioural measures of interest were the estimation errors and the size of the updates. For each participant, the difference between the first and second estimate was computed in each of the 60 trials, and then mean updates were computed separately for each of the four experimental conditions (s_p, s_n, ns_p, ns_n) by averaging all trial-based updates within each condition. Thus, every participant had four repeated measures of mean updates. If present, trials with missing responses (M = 1.05, SD = 2.70 across the sample) and trials with estimation error of zero (M = 2.40 SD = 3.57; when the participants' first estimate was 1% no errors can be generated to provide desirable base rates, i.e. rates lower than the first estimate) were excluded before computing mean updates. We used signed update values with a differential procedure for lower (positive) and higher (negative) base rates. In conditions s_p and ns_p, updates in each trial were computed as first estimate minus second estimate, because the presented base rate was lower than the first estimate and second estimates were expected to be adjusted to this smaller value (Kuzmanovic et al., 2015; Sharot et al., 2011). Conversely, in conditions s_n and ns_n, updates were computed as second estimate minus first estimate. For trials in which participants responded in an unexpected direction (e.g. first estimate = 20%, base rate = 10%, second estimate = 25%) update was a negative value. Mean update scores were entered into a mixed ANOVA with two within subject factors type (social vs non-social) and valence (positive and negative) and one between subject factor schizotypy (high vs low). Analysis were performed with R.

For each event in each session, an estimation error term was calculated as the absolute difference between the participant's first estimate and the corresponding base rate presented:

$$\text{Estimation Error} = |\text{ First Estimate} - \text{Base Rate Presented}|$$

To explore the relationship between estimation errors and update, for each participant, two linear regressions were conducted entering estimation errors as independent variables and updates as dependent variables – one for trials in which participants received positive news and one for trials in which participants received negative news. Thus, we defined two learning scores for each participant (one for positive and one for negative news) as the regression coefficients corresponding to the slope in each regression. Schizotypy SPQ scores were entered as continuous variables, analysis was carried out with R.

4.2.6. Imaging acquisition

Scanning was performed on a 3T Siemens Magnetom TIM Trio scanner using a 32-channel head coil at the Combined Universities Brain Imaging Centre. A structural scan was acquired for co-registration of the EPI data by means of a weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MP Rage; repetition time 1900s; 1mm x 1mm 1mm voxel size; in plane resolution of 256 x 256 x 176 slices, scanning time approximately 5 minutes). fMRI data during the update experiment were acquired in two sessions with a T2*-weighted gradient echo planar imaging sequence (repetition time: 2s , echo time: 30ms, flip angle: 78° , 2.5 x 2.5 x 2.5 voxel size, 204mm field of view , 80 x 80matrix size, 52 axial sections collected with multiband interleaved ascending acquisition, parallel in-plane reduction factor of 2). Stimuli and response displays were presented and recorded by the software PsychoPy2 (Peirce, et al., 2019) and projected onto a screen at the end of the magnet bore that participants viewed via a mirror mounted on the head coil.

4.2.7. Imaging preprocessing

Data was preprocessed following the recommended pipeline for the analysis of Connectomes (C-PAC; Craddock et al., 2013). The anatomical image was deobliqued using 3drefit in the Analysis of Functional NeuroImages (AFNI) framework (https://afni.nimh.nih.gov) and reoriented into RPI using AFNI's 3dresample. Skull stripping was performed with AFNI's 3dSkullStrip. FSL FLIRT was used to perform a linear transformation of the skull stripped image into 2mm Montreal Neurological Institute (MNI) template space (Jenkinson, Bannister, Brady, & Smith, 2002). The registration was then refined using non-linear transformation performed by FSL FNIRT (Andersson, Jenkinson, & Smith, 2007). The skull stripped normalised T1 was segmented using FSL FAST (Zhang, Brady, & Smith, 2001). Tissue masks for the cerebrospinal fluid (CSF), white matter (WM) and grey matter (GM) were created using FSL and the following procedure: registering the tissue template in MNI space to native space using FSL prior tissue probability maps, finding overlap between the tissue probability maps and the tissue template created in the previous step, applying a 0.4 threshold and binarizing the tissue templates, and finally generating the tissue masks by applying the prior in native space to the binarized tissue probability map.

The EPI images were deobliqued and reoriented into RPI using AFNI, and slice time correction was performed with AFNI's 3dTshift. AFNI's 3dTstat was used to obtain mean intensity values over all timepoints for each voxel (base image). Two pass motion correction was performed on the data using AFNI's 3dvolreg. For each volume the image was aligned with the base mean image, providing motion displacement and movement parameters. Voxel wise statistics for the motion corrected output from this step were used as the base for the second pass motion correction using 3dvolreg and a Fourier transformation to obtain the motion and displacement parameters. The images were registered to the subject's T1 scan using

FLIRT, and subsequently normalised to MNI space. The normalized images were smoothed with AFNI's 3dmerge using a 6mm FWHM kernel. Nuisance regression to remove noise signals from the data was performed using AFNI's 3dDeconvolve and 3dTproject. For this step, the motion parameters were demeaned, and motion parameter derivatives were calculated. The CSF and WM masks were resampled into functional space using AFNI's 3dresample and respective time courses were extracted. The demeaned 6 motion parameters, the 6 motion derivatives and the CSF and WM signal were regressed out of the data with AFNI. Subjects with motion exceeding 3mm were removed from the neuroimaging sample, resulting in a total sample of 23 participants in the HS group and 24 participants in the LS group (the behavioural data from these subjects was still used). A comparison of the mean framewise displacement (FD; Power, Barnes, Snyder, Schlaggar, & Petersen, 2012) between the final HS and LS groups revealed no significant difference in head motion between the groups ($t = 0.34$, $p = 0.78$).

4.2.8. fMRI Data Analysis

We conducted a linear parametric modulation analysis of the neural activity during the presentation of base rates by estimation errors. For first level models, for each participant, we created a design matrix with event onsets time-locked to the temporal positions of event presentation (duration 3s), presentation of cue prompting response (duration equal to response time), presentation of base rate (duration 2s), presentation of cue prompting response for second estimate (duration equal to response time). These regressors were separately modelled for the different experimental conditions, as per previous work with this task (Kuzmanovic, Jefferson, & Vogeley, 2015; Kuzmanovic, Jefferson, & Vogeley, 2016; Kuzmanovic, Rigoux, & Vogeley, 2019). Button presses indicating the first and the second estimate were modelled on separate regressors (duration from the onset of the response event to the last button press).

Trials with missing responses, and trials with estimation error of zero, if present, were modelled on a separate regressor. Movement parameters were included as multiple regressors of no interest. To validate the social manipulation, we included 2 contrasts for the event presentation of i) social and ii) non-social events (i.e. event presentation screen that lasted 3s and during which participants were asked to think about the event). To compare our findings with previous work, we included 2 contrasts for tracking i) positive EE and ii) negative EE (time locked to base rate presentations in the respective conditions with absolute estimation errors as parametric modulators; Sharot et al., 2014). To identify brain regions tracking presentation of disconfirming new evidence and estimation errors, we entered absolute estimation errors as parametric regressors during the presentation of base rates for the 4 separate conditions, resulting in 4 contrasts (s_p, s_n, nons_p, nons_n). We were also interested in identifying regions differentially tracking estimation errors for the separate conditions, thus we included 4 contrasts for the i) social, ii) non-social, iii) positive and iv) negative conditions as well. This gave us a first level design matrix (within session analysis) with 12 contrasts of interest, each contrast weighted a single regressor of interest with 1 and all other regressors with 0. Regressors were convolved with a canonical hemodynamic response function (HRF) and its time derivative.

For second level models (between-session analysis), we inputted the data from first level contrasts (i.e. the respective contrasts of interest) and, for each subject, we combined the two runs of the task to model the subject's mean response using fixed effects in FSL Feat. At the group level, we identified regions that exhibited increased activation in response to the social presentation of events vs the non-social presentation (social > non-social), and regions that exhibited higher activity in the non-social conditions (non-social vs social) to control or function not related to social activity. To compare results with previous studies, we identified regions where the BOLD signal correlated with absolute estimation errors for either positive

trials or negative trials. To investigate group differences for the separate task conditions we used independent samples t-test (as the interaction terms for the within subject factors were set out at the first level). We investigated HS > LS and vice versa to identify the neural activity correlating with tracking estimation errors for the social, non-social, positive and negative trials relative to baseline. We also investigated group differences to identify regions specifically tracking estimation errors during updating for the interaction terms – social positive trials, social negative trials, non-social positive trials and non-social negative trials. These contrasts (validation and group differences) contrasts were carried out compared to the task baseline and had estimation errors as parametric modulators thus scaling activity to the behavioural measure. Higher-level analysis was carried out using FLAME (FMRIB's Local Analysis of Mixed Effects) stage 1 (Beckmann, Jenkinson, & Smith, 2003; Woolrich, 2008; Woolrich, Ripley, Brady, & Smith, 2001). Results were considered significant at a cluster threshold of Z (gaussianised T/F statistic) > 2.3 and a corrected cluster significance threshold of $p < .05$ Random Field Theory-applied Family-Wise Error correction (Woolrich, 2008).

4.3. Results

4.3.1. Demographics and questionnaires

Table 1 summarizes the sociodemographic characteristics of each group. HS and LS groups were matched for Gender, Age and IQ (measured by WASI II) but differed on all schizotypy measures. Specifically, HS had higher scores on the SPQ total score and on each of the three factors comprising the SPQ.

Table 1. Demographic and questionnaire data across LS and HS groups.

Characteristic	LS (n = 26)	HS (n=27)	t/χ2	p
Gender(male/female)	7/19	10/17	0.55	0.40
Age (years)	20.63 (SD = 2.20)	19.51(SD= 1.25)	1.10	0.31
IQ score	93.78(SD = 9.20	95.12 (SD = 9.26)	0.63	0.52
SDS	5.96 (SD = 1.52)	4.86 (SD = 2.33)	1.86	0.07
SPQ Total	7.61 (SD = 3.60)	46.64 (SD = 5.23)	-29.25	< 0.01
SPQ Cognitive Perceptual Factor	2.83 (SD= 2.01)	20.41 (SD = 5.22)	-15.02	< 0.01
SPQ Interpersonal Factor	3.57 (SD = 2.48)	20.86 (SD = 4.44)	-16.22	< 0.01
SPQ Disorganised Factor	1.91 (SD = 2.42)	10.77 (SD = 2.82)	-11.29	< 0.01

4.3.2. Behavioural results by update size

Sample characteristics by group distribution are presented in Table 2. Certain group distributions violated the assumptions of normality (see Table 2) thus non-parametric tests were used to analyse the data. We included schizotypy (high vs low) as a between-subjects factor, and type (social vs non-social) and valence (positive vs negative) of events as within-subject

factors. The nparLD package in R was used to analyse the nonparametric data (Domhof & Langer, 2002; Noguchi, Gel, Brunner, & Konietschke, 2012).

Table 2. Descriptive statistics of the group distributions in the data. W refers to Shapiro-Wilk test of normality.

Distribution by group			M	SD	Skewness	Kurtosis	W	p
Sch	Type	V						
H	NS	N	-0.86	0.68	-0.9	-0.1	0.9	0.01
L	NS	N	-0.68	1.42	1.3	1.47	0.86	< 0.01
H	S	N	1.42	0.97	0.22	-0.5	0.97	0.5
L	S	N	1.22	1.61	-1.58	5.26	0.81	<0.01
H	NS	P	1.37	1	-0.17	-0.43	0.98	0.87
L	NS	P	1.63	1.84	0.49	0.14	0.97	0.57
H	S	P	1.32	1	0.52	-0.57	0.95	0.27
L	S	P	1.56	1.27	-0.67	1.78	0.89	<0.01

Sch - Schizotypy (H -high; L -low). V - Valence (N - negative; P - positive). Type (NS - non-social; S - social).

Results indicated that there is a significant main effect of social type ($F(1,59) = 53.02$, $p < 0.01$) and valence ($F(1,59) = 52$, $p < 0.01$), as well as a significant interaction between these factors ($F(3,59) = 43.38$, $P < 0.01$; Fig 2). No other effects reached significance. Wilcoxon signed rank test revealed that people update less in the non-social compared to the social

conditions, V = 1103, p < 0.01; and in the negative compared to the positive conditions, V = 1119.5, p < 0.01 but this affect did not differ between LS and HS groups.

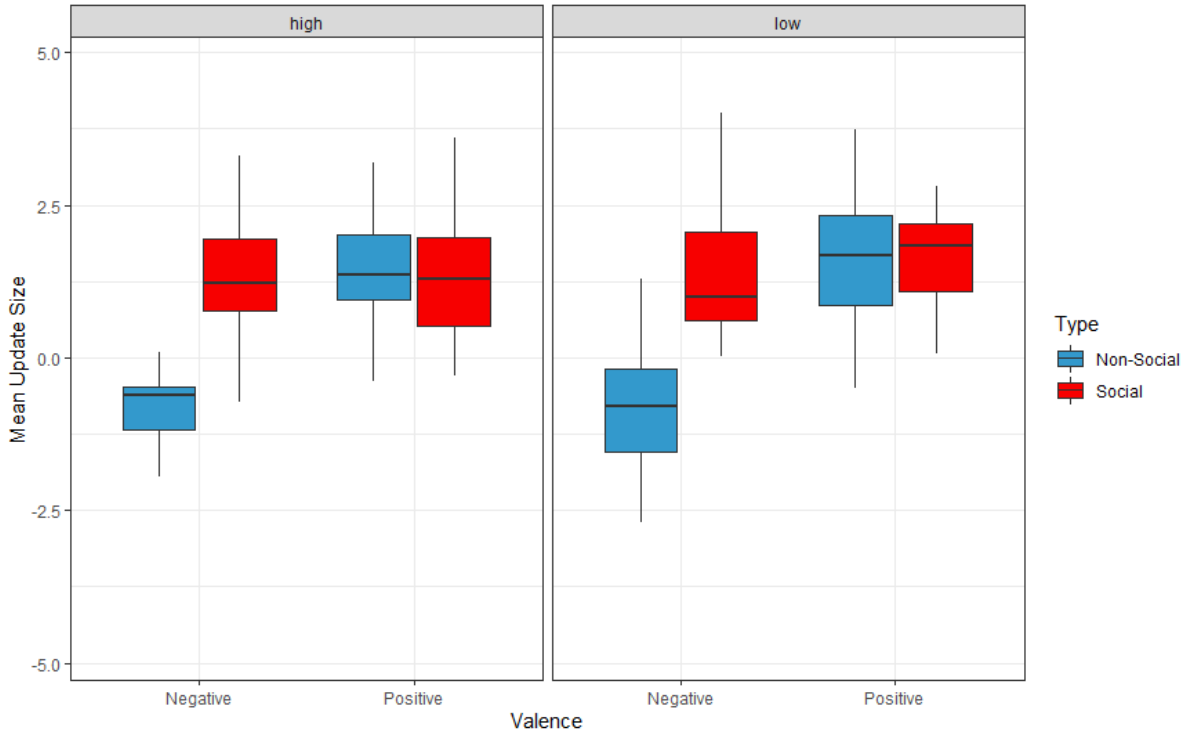

Fig 2. Bar chart of mean update size by conditions and groups.

4.3.3. Behavioural results by learning scores

To explore the relationship between estimation errors and update, for each participant, two linear regression models were conducted, one model for positive conditions (when participants received good news) and one model for negative conditions (when participants received bad news). For every model we entered estimation errors as independent measures and updates as dependent measures. Thus, we defined two learning scores for each participant

(one for good and one for bad news) as the regression coefficients corresponding to the slope in each regression.

Descriptive statistics for the separate trials (positive vs negative) are presented in Table 3. Due to deviation from the normal distribution, we employed the Kendall–Theil Sen Siegel nonparametric linear regression with the mblm package in R (Fernandes & Leblanc, 2005). The approach uses median sloping lines that are computed between each and every of the two points in a dataset.

Table 3. Descriptive statistics of the group distributions in the data. W refers to Shapiro-Wilk test of normality.

Event type	DV	M	SD	Skewness	Kurtosis	W	p
Positive	Update size	1.46	1.11	0.03	0.87	0.99	0.34
Positive	Estimation Error	2.52	5.55	-1.20	1.24	8.97	< 0.01
Negative	Update size	0.28	1.58	0.01	-0.01	0.99	0.52
Negative	Estimation Error	6.4	9.85	-2.74	3.98	9.38	<0.01
Social	Update Size	1.37	1.26	0.08	0.5	0.78	0.24
Social	Estimation Error	1.55	1.38	-2.59	1.54	6.98	< 0.01
Non-Social	Update Size	0.36	1.58	0.04	-0.01	0.81	0.43
Non-Social	Estimation Error	1.61	1.25	-2.41	2.15	8.51	< 0.01

There was no association between estimation errors and update sizes for negative events, V = 29, p = 0.72, residual standard error (indicating the quality of the regression fit) was 1.61. For positive events, estimation errors were a significant predictor for update size, V = 53, p < 0.01, suggesting that participants utilised the information presented to them only in conditions presenting good news (Fig 3). Estimate for the model (slope = 0.82) indicates a positive relationship between predictor and outcomes, with a residual standard error of 0.95. Estimation errors were significant predictors for subsequent update sizes in both social (V = 0.42, p < 0.01, slope = 0.21, residual standard error = 1.25) and non-social conditions (V = 0.56, p < 0.01, slope = 0.89, residual standard error = 1.12, Fig 4).

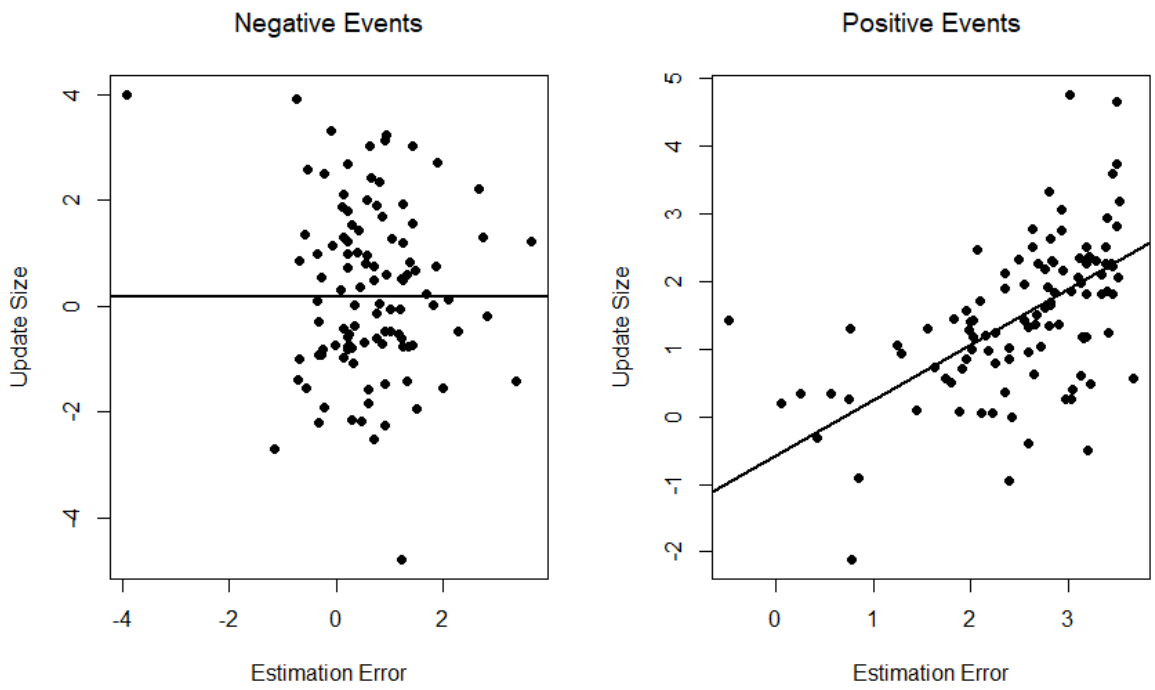

Fig 3. Scatterplots of the relationship between update size and estimation error based on valence.

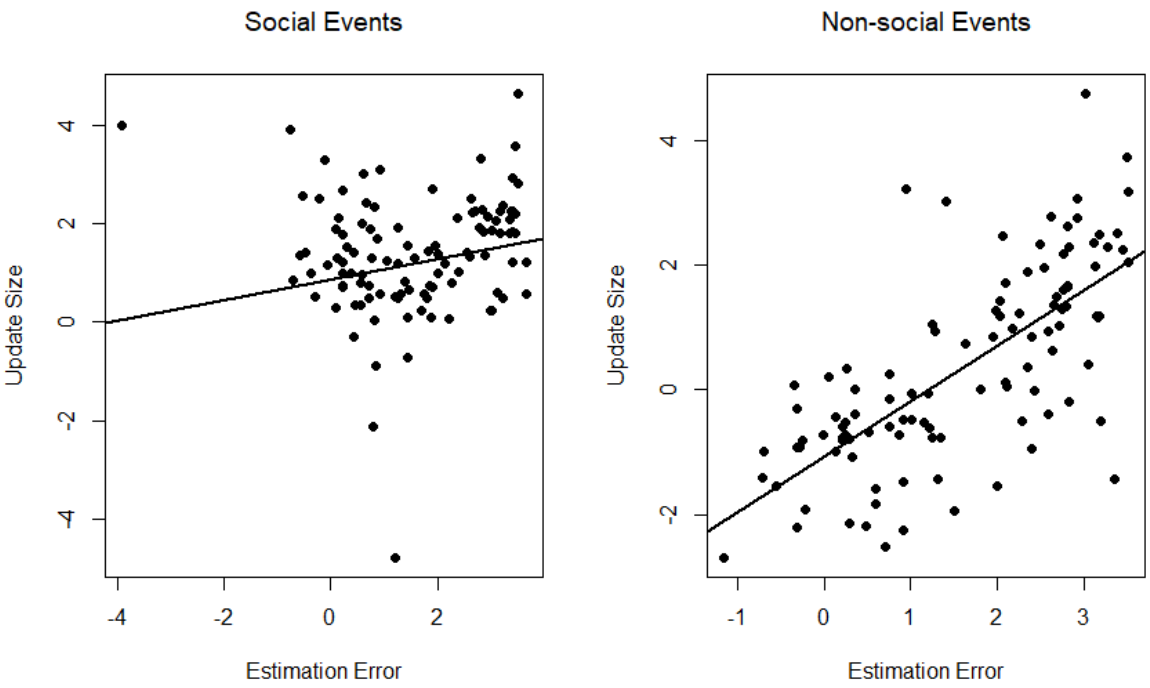

Fig 4. Scatterplots of the relationship between update size and estimation errors based on type of event.

4.3.4. fMRI data – task validation

We used one-sample t-tests to identify regions showing distinct activation patterns for social and non-social events across all participants (i.e. response to the event presentations). For non-social events, there was greater activity in the left SFG, orbitofrontal cortex (OFC), insular cortex and IFG (see table 4). Relative to non-social event, social events were associated with greater activity in the left IFG, posterior cingulate cortex (PCC), middle temporal gyrus (MTG), superior temporal gyrus (STG), amygdala, inferior temporal gyrus (IFG) and in the bilateral precuneous cortex and temporal fusiform gyrus (see table 4; Fig 5).

Table 4. Regions of activation during the event presentation of social vs non-social conditions.

Brain Region	Side	MNI			Number of voxels	Z-score	P-value FWE
		x	y	z			
Social Events > Non-Social events							
IFG	L	-51	22	-1	42	2.6	<.002
PCC	L	-8	-50	34	356	3.99	<.001
Precuneous cortex	B	-4	-60	28	124	3.99	<.001
MTG	L	-53	-11	-16	149	3.96	<.001
STG	L	-56	6	-13	39	2.9	<.001
Amygdala	L	-22	-2	-23	19	2.4	<.001
ITG	L	-46	-42	-23	79	3	<.001
Temporal Fusiform Gyrus	B	-39	-43	-24	27	3.2	<.001
Non-Social Events > Social Events							

SFG	L	-10	21	61	86	3.4	<.001
OFC	L	-33	28	-16	182	3.1	<.001
Insular Cortex	L	-28	16	-10	107	3.5	<.002
IFG	L	-45	20	8	31	3.2	<.01

4.3.5. fMRI data – comparison to previous work

To compare our results to previous research with this task, we used one-sample t-tests to identify brain regions tracking estimation errors for positive vs negative news (estimation errors were entered as parametric regressors) The right MFG, IFG, SFG and insular cortex showed greater activity in response to estimation errors from positive conditions. The regions showing greater activation to estimation errors from negative events were the same, with the exclusion of the insular cortex (see Table 5).

Table 5. Regions of activation tracking response to estimation errors in the positive and negative conditions.

Brain Region	Side	MNI			Number of voxels	Z-score	P-value FWE
		x	y	z			
Positive EE							
MFG	R	40	48	-12	185	5.8	<.002
MFG	R	45	19	32	481	3.7	<.001
IFG	R	50	19	4	41	3.1	<.001
SFG	R	10	38	37	121	3.9	<.001
Insular Cortex	R	35	19	-9	174	3.8	<.001
Negative EE							
SFG	R	7	34	45	304	4.6	<.001
MFG	R	43	10	45	271	4.8	<.001
MFG	R	47	45	-10	75	4.3	<.002
IFG	R	51	23	4	51	2.9	<.001

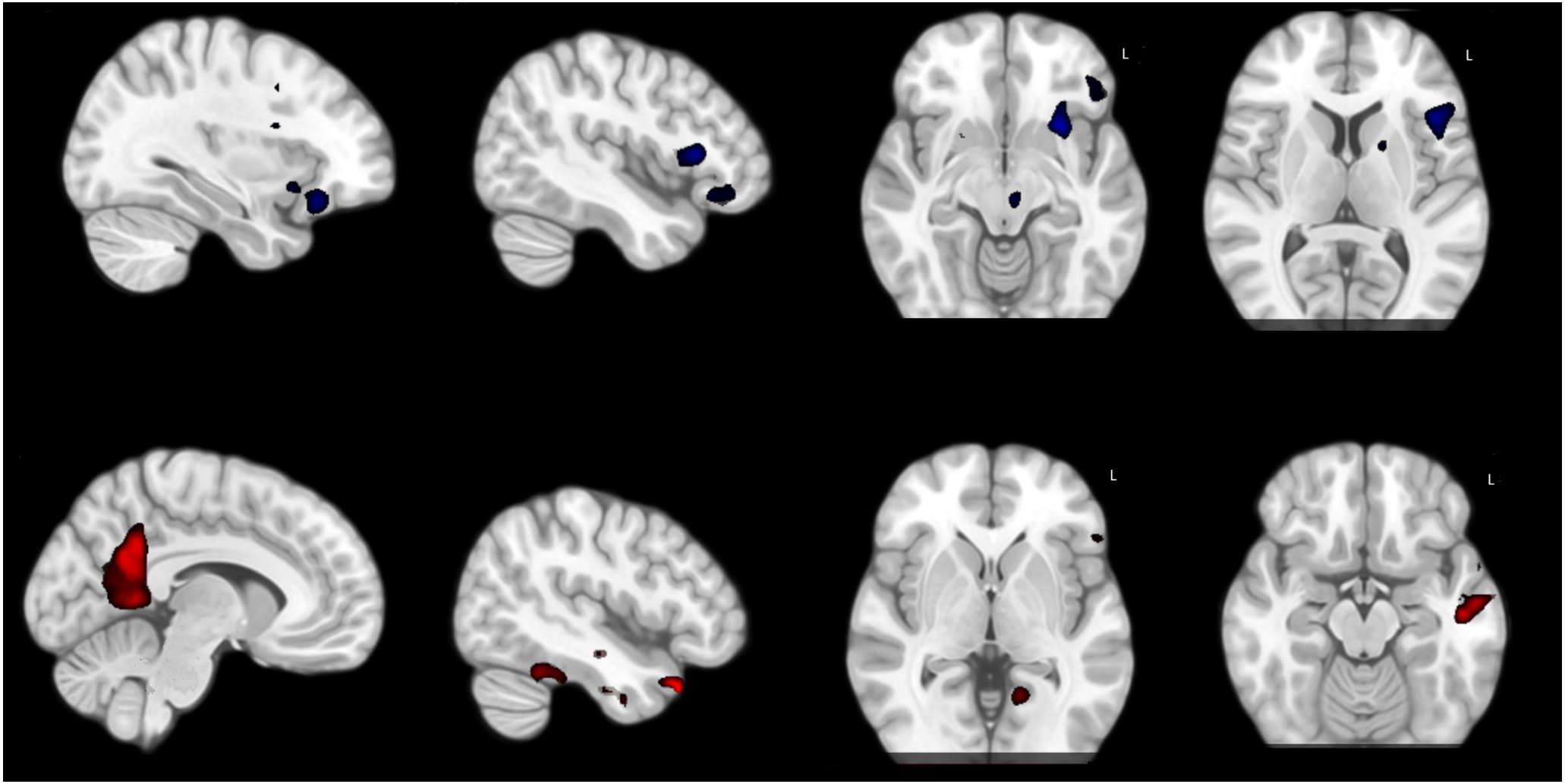

Fig 5. Activations patterns for non-social (top row, blue colour) and social (bottom row, red) event presentations. Activations for the IFG, OFC and insular cortex for non-social events. Activations in the PCC, precuneous cortex, MTG, temporal pole and temporal fusiform gyrus for social events.

4.3.6. fMRI data, group differences by condition

To investigate the main effects of conditions (social vs. non-social and positive vs. negative conditions), we applied independent sample t-test to compare brain activity between HS and LS groups for regions tracking estimation errors (see Table 6). For social estimation errors relative to baseline, HS subjects showed greater activity in the ventromedial PFC (vmPFC) and reduced activity in the MFC compared to LS participants. Relative to LS participants HS participants showed reduced activity in the ventral stiatum (VS), the insular cortex, the parahippocampal gyrus, the MFG and the IFG during tracking of non-social estimation errors; and reduced activity in the VS, MFC and IFG in response to positive prediction errors. In response to estimation errors in the negative conditions, HS participants showed greater activity in the right IFG and the vmPFC, and reduced activity in the left IFG, MFC, parahippocampal gyrus, caudate and PCC.

Table 6. Group differences of regions of activation for the individual conditions (with estimation errors as parametric modulators) as relative to baseline.

Brain Region	Side	MNI			Number of voxels	Z-score	P-value FWE
		x	y	z			
Social EE							
HS > LS							
vmPFC	L	-34	49	2	47	2.7	<.002
LS > HS							
MFC	R	8	56	10	27	2.8	<.001
MFC	L	-17	55	17	31	2.8	<.001
Non-Social EE							
LS > HS							
VS		-11	2	10	52	2.7	<.001

Parahippocampal Gyrus	L	-27	-18	-28	29	3.2	<.001
MFC	R	4	63	-4	27	2.8	<.01
MFC		6	42	45	123	2.9	<.01
IFG	L	-35	25	7	81	3.2	<.001
Insular cortex		34	24	-4	93	2.6	<.01
Positive EE							
LS > HS							
VS	L	-11	2	10	34	2.6	<.001
MFC	L	-13	47	43	76	2.8	<.001
IFG	L	-35	24	7	79	2.4	<.001
Negative EE							
HS > LS							
IFG	R	39	10	46	39	2.6	<.01
vmPFC	R	33	48	0	68	2.6	<.01

LS > HS							
IFG	L	-34	23	-16	76	3.2	<.01
MFC	L	-17	47	43	62	2.7	<.01
MFC	R	3	63	-3	28	2.4	<.01
Parahippocampal Gyrus		-26	-18	-29	47	3	<.01
Caudate	L	-8	16	0	17	2.4	<.01
PCC	L	-4	-43	8	37	2.8	<.01

4.3.7. fMRI data, group differences, interactions

Four interaction contrasts defined at the first level and we used in independent samples t-tests at the second level to examine group differences in tracking prediction errors (Table 7, Fig 6). Relative to LS participants, during the social positive condition, the HS group showed grater activity in the right vmPFC and the left IFG and reduced activity in the left dlPFC. Grater activity in the right vmPFC was also observed in HS individuals in response to social negative estimation errors. There were no differences between the groups in response to non-social negative events, but the LS subjects displayed greater activity in the IFG during non-social positive trials.

Table 7. Group differences of regions of activation for the social and non-social conditions (with estimation errors as parametric modulators).

Brain Region	Side	MNI			Number of voxels	Z-score	P-value FWE
		x	y	z			
Social Positive EE							
HS > LS							
vmPFC	L	-17	57	17	41	2.8	<.001
IFG	L	-39	34	-10	39	2.9	<.001
LS > HS							
dlPFC	L	-39	55	15	32	3.4	<.001
Social Negative EE							
HS > LS							
vmPFC	R	40	47	-8	81	3.7	<.001

Non-Social Positive EE						
LS > HS						
IFG	34	24	8	52	3.5	<.001

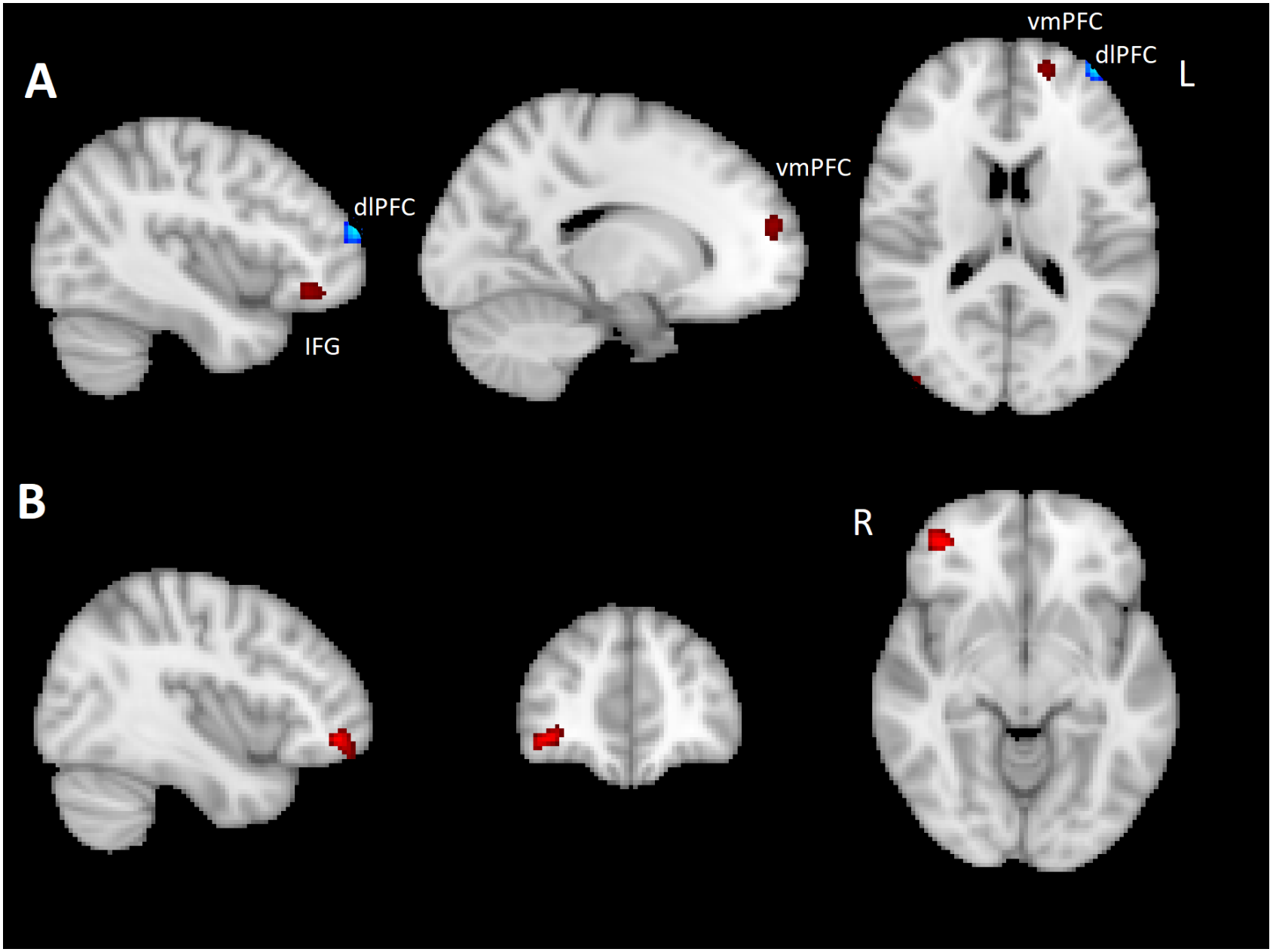

Fig 6. Group differences for the social positive trials (panel A) and social negative trials (panel B). Red colour indicates higher activity in the HS compared to the LS group, blue colour indicates higher activity in the LS compared to the HS.

4.4. Discussion

We utilised a modified version of a well-validated belief-updating task (in that we investigated social vs non-social events as well) to investigate the learning behaviour of high schizotypy vs low schizotypy individuals in the context of social information. Replicating previous work, our sample exhibited an optimism bias (updating beliefs more in response to desirable news). Furthermore, in line with previous fMRI studies using the belief-updating task, the IFG and MFG were identified as key regions tracking estimation errors during belief updating in this paradigm. There were no behavioural differences between the LS and HS groups. As hypothesised, group analyses indicated that high schizotypy participants showed abnormal activity in prefrontal regions during social belief updating. Specifically, in HS individuals, compared to LS individuals, we observed increased activity in the vmPFC and the left IFG, and lower activity in the dlPFC in response to social positive and negative prediction errors. In comparison, in LS participants, non-social errors (positive or negative conditions) were associated with increased activity in a number of prefrontal and midbrain regions. Overall, the current findings indicate that HS participants show increased PFC response to socially salient prediction errors in HS individuals as well as altered neural activity in response to non-social prediction errors, as observed in previous work (Corlett & Fletcher, 2012).

As hypothesised, we replicated the optimism bias observed in previous studies with this paradigm (Garrett et al., 2014; Garrett & Sharot, 2017; Kuzmanovic et al., 2015; Kuzmanovic & Rigoux, 2017; Sharot et al., 2011; Sharot et al., 2012; Sharot & Garrett, 2016) indicating that subjects update more in response to positive news. This is complemented by, estimation errors for positive trials that predict subsequent update size, suggesting that participants utilised the information presented to them to inform their future beliefs. In contrast, there was no association between estimation errors and update sizes for negative trials, suggesting abnormal

learning patterns where participants tend to ignore negative information (Garrett & Sharot, 2017; Sharot & Garrett, 2016). Interestingly, participants updated more in response to the social conditions compared to the non-social conditions. These findings suggest that the biased weighting of information characterizing the optimism bias might not extend to socially relevant events, as valence (good or bad news) did not affect the updating in response to social information. This result supports our hypothesis that social information is of particular importance beyond non-social information (Adolphs, 2001; Adolphs, 2003a; Adolphs, 2003b; Adolphs, 2009). Numerous studies have shown that humans display an attentional bias towards faces or other human features (Bindemann, Burton, Hooge, Jenkins, & de Haan, 2005; Gamer & Büchel, 2009; Mack, Pappas, Silverman, & Gay, 2002; Ro, Russell, & Lavie, 2001; Shelley-Tremblay & Mack, 1999; Theeuwes & Van der Stigchel, 2006; Vuilleumier, 2000) and these social stimuli are prioritized even when there is competition with other salient objects in naturalistic scenes (Birmingham, Bischof, & Kingstone, 2009; End & Gamer, 2017; Fletcher-Watson, Findlay, Leekam, & Benson, 2008). The processing of social information is also thought to be reflexive (Bindemann et al., 2005; Bindemann, Burton, Langton, Schweinberger, & Doherty, 2007; Deaner & Platt, 2003; Langton, Watt, & Bruce, 2000; Ristic & Kingstone, 2005) with social features prioritized as early as the first eye saccade after stimulus presentation (Rösler, End, & Gamer, 2017). Thus, the current findings extend previous work by demonstrating that social salience also affects learning rates for future outcomes.

The social events in our task activated a number of cortical and subcortical regions associated with the processing of social information, such as the amygdala, the PCC, the precuneus, the lateral temporal cortex and the IFG (Table 4). The amygdala is found to activate during recognizing emotional facial expressions, an initial finding that has been followed by a large literature documenting the amygdala's involvement in both appetitive and aversive emotional processing (Adolphs, 2003a; Adolphs, 2009; Aggleton & Young, 2000). The

posterior cingulate cortex is activated in theory-of-mind tasks and its activation likely involves generating knowledge of both our own mind and the minds of others (Saxe & Kanwisher, 2003; Saxe & Powell, 2006). The precuneus has been involved with self-consciousness processes, such as reflective self-awareness, that involve rating one's own traits compared to those judged of other people (Kjaer, Nowak, & Lou, 2002; Lou et al., 2004). The lateral temporal cortex (including lateral and inferior portions of the temporal lobes, the temporal poles, and the superior temporal gyrus) is particularly relevant to social cognition of semantic and perceptual processes, such as constructing stereotypes, individual impressions and dispositional attributions (Hart et al., 2000; Lieberman, Gaunt, Gilbert, & Trope, 2002; Mitchell, Heatherton, & Macrae, 2002; Satpute & Lieberman, 2006). Here, we found activations of inferior portions of the temporal cortex, temporal poles and the STG for social vs non-social events. The STG is a key structure for social cognition, as it is sensitive to recognition of other people, the actions they perform and for positing intentions (Satpute & Lieberman, 2006). Similarly, the MTL (particularly the anterior part as observed here), has been linked to memory for emotional events (Dolcos, LaBar, & Cabeza, 2004; LaBar & Cabeza, 2006) and attribution of intentions (Brunet, Eric, Sarfati, Hardy-Baylé, & Decety, 2000). The fusiform gyrus is a large region in the inferior temporal cortex that plays important roles in object and face recognition, and recognition of facial expressions is located in the fusiform face area (FFA; Kleinhans et al., 2008; Pelphrey, Morris, McCarthy, & LaBar, 2007; Perlman, Hudac, Pegors, Minshew, & Pelphrey, 2011; Pierce & Redcay, 2008). Finally, the IFG was activated during the presentation of social events. While this area is associated with emotional empathy (Shamay-Tsoory, Aharon-Peretz, & Perry, 2009) it is also widely associated with language processing (Binkofski et al., 1999; Brannen et al., 2001; Fiebach, Friederici, Müller, & Cramon, 2002; Heim et al., 2005; Opitz, Müller, & Friederici, 2003; Sahin, Pinker, & Halgren, 2006). It is possible that this region is be highly active in response to descriptions of non-social events, alongside the

SFG and the OFC (Chou et al., 2006; Demb et al., 1995; Fox et al., 2000; McDermott, Petersen, Watson, & Ojemann, 2003; Shuster & Lemieux, 2005). In summary, the presentation of non-social events in our task was associated with activity in frontal cortex regions responsible for language processing. The presentation of the social events activated a broader network of regions involved with emotion processing and memory, intentions and attributions, suggesting the events were perceived as socially salient.

For the final validation of our task, we identified regions activated by estimation errors for either positive or negative trials across all participants. Mirroring previous investigations using similar task designs, we found that neural activity for estimation errors during positive events were associated with IFG, MFG and SFG, and that activity estimation errors for negative events was associated with SFG and IFG (Garrett et al., 2014; Sharot et al., 2011). The IFG, activated in both valence conditiond is important for flexibly altering beliefs and it has been found to play a role in reversal learning (Cools et al., 2002) and to track and integrate information into prior beliefs (Sharot et al., 2011). This region is also thought to play different roles in inhibition (Aron et al., 2004), such as response/action inhibition (Bunge, Dudukovic, Thomason, Vaidya, & Gabrieli, 2002), task-switching (Dove, Pollmann, Schubert, Wiggins, & Von Cramon, 2000), inhibition of unwanted memories (Anderson et al., 2004) and inhibition of working memory to resolve interference from previous trials (D'Esposito, Postle, Jonides, & Smith, 1999). The activation found here thus matches previous work using belief-updating tasks and further supports the role of the IFG in inhibiting unwanted news from altering beliefs. The MFG and the STG have also been found to activate in response to tracking estimation errors in different contexts, including errors resulting from incorrect responses (Greening, Finger, & Mitchell, 2011), errors in expectations in the absence of action (Yeung, Holroyd, & Cohen, 2005), reversal errors (Cools et al., 2002; Mitchell et al., 2009) and prediction errors that code differences between expectations and outcomes (Taylor, Stern, & Gehring, 2007). In

addition, we found that the insula was also activated specifically when tracking positive prediction errors (i.e. trials on which participants received good news). Studies have suggested this brain region is involved with motivational decision making, namely processing, representing and learning information about risk and uncertainty (Huettel, Stowe, Gordon, Warner, & Platt, 2006; Kuhnen & Knutson, 2005; Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003; Preuschoff, Quartz, & Bossaerts, 2008; Singer, Critchley, & Preuschoff, 2009). This fits in well with the behavioural findings that subjects update more, and thus learn more, from positive estimation errors specifically. In summary, the results we obtained using this modified version of the task match previous findings suggestion the paradigm used here was suitable for assessing the neural correlates of belief-updating in people with high and low schizotypy.

HS individuals were characterised with higher neural activity, compared to LS individuals, in the right vmPFC and the left IFG during social positive and social negative trials. We found no areas of hyperactivation in HS subjects in non-social interaction conditions relative to LS subjects. The right vmPFC is a key region responsible for social conduct, decision-making and emotional processing (Tranel, Bechara, & Denburg, 2002). Clinical observations and experimental studies indicate that patients with vmPFC lesions show altered emotional and social behaviour by developing severe impairments in personal and social decision making, despite intact intellectual abilities (Bechara, Damasio, Damasio, & Lee, 1999; Blair & Cipolotti, 2000; Dimitrov, Phipps, Zahn, & Grafman, 1999). After vmPFC brain injury, patients often demonstrate acquired social conduct deficits such as an inability to respond appropriately to social cues in the environment or failure to obey conventional social rules (Milne & Grafman, 2001), with some researchers suggesting this area is likely the repository of social knowledge that is required for managing interpersonal interactions (Grafman, 1995). Meta-analyses of fMRI data also indicate a role for vmPFC in ToM ability (Molenberghs,

Johnson, Henry, & Mattingley, 2016; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014). A main aspect of social cognitive function putatively sub served by the vmPFC is processing of self-relevant information (Northoff et al., 2006; Svoboda, McKinnon, & Levine, 2006). Self-referential processing is important for social cognitive functioning, as interacting with others requires reflection on our own feelings and knowledge (Mitchell, Banaji, & MacRae, 2005; Vogeley & Fink, 2003). Difficulties in self-referential and introspective processing have been observed in schizophrenia patients across various paradigms (Ditman & Kuperberg, 2005; Fisher, McCoy, Poole, & Vinogradov, 2008; Parnas & Sass, 2001; Seal, Aleman, & McGuire, 2004). Furthermore, studies reliably report that the Default Mode Network (DMN) shows coherent intrinsic activity and is implicated in self-referential and introspective processes; (Buckner, Andrews-Hanna, & Schacter, 2008; Mason et al., 2007). Patients with schizophrenia show widespread alteration in DMN activity and connectivity (Bluhm et al., 2007; Camchong, Bell, Mueller, & Lim, 2011; Liu et al., 2006; Repovs, Csernansky, & Barch, 2011; Rotarska-Jagiela et al., 2010; Salvador et al., 2010; Zhou et al., 2007 thought to contribute to the difficulties in self-referential and introspective processing (Bluhm et al., 2007; Camchong et al., 2011; Liu, Hairston, Schrier, & Fan, 2011; Zhou et al., 2007).

In the context of the current task, vmPFC activity could reflect self-referential processes as the task requires participants to consider the average base rates of events in the context of judging the likelihood of these events happening to themselves. We speculate that the higher vmPFC activity in HS subjects indicates that the prefrontal cortex in these individuals is particularly sensitive to self- and other- referential processing and has to exert higher levels of activity to achieve a behavioural performance similar to that of controls. This interpretation fits in with clinical cases, where research consistently finds that schizophrenia is associated with functional and behavioural deficits during various social cognitive and self-referential tasks activating the vmPFC (Honea, Crow, Passingham, & Mackay, 2005; Hooker, Bruce, Lincoln,

Fisher, & Vinogradov, 2011; Park, Park, Chun, Kim, & Kim, 2008; Pomarol-Clotet et al., 2010; Williams, 2008). The findings also fit in with a number of previous schizotypy investigations that have reported increased prefrontal cortex activity in response to socially salient cues (Kozhuharova et al., 2020; Modinos et al., 2010b; Modinos et al., 2011; Mohanty et al., 2005). Furthermore, we show that HS individuals also present with higher activity in the left IFG in response to estimation errors for social events, but not for non-social positive or negative interaction conditions. The IFG tracks and integrates information into prior beliefs (Garrett et al., 2014; Sharot et al., 2011). The greater IFG activity in response to socially salient estimation errors might reflect a higher effort to integrate social information into prior beliefs in order to achieve normal behavioural performance.

The vmPFC is not only a key region for social cognition but is also involved with value-based decision making (Bechara, Damasio, & Damasio, 2001). Subsequent studies of vmPFC lesion patients have documented value-based decision-making deficits in a wide variety of paradigms, including risky gambles (Camille et al., 2004; Pujara, Wolf, Baskaya, & Koenigs, 2015), probabilistic reinforcement learning (Fellows & Farah, 2003; Wheeler & Fellows, 2008), economic exchange (Koenigs & Tranel, 2007; Krajbich, Adolphs, Tranel, Denburg, & Camerer, 2009) and simple binary item preference (Henri-Bhargava, Simioni, & Fellows, 2012). In parallel with these demonstrations of decision-making deficits among vmPFC lesion patients, human functional imaging studies have linked vmPFC activity with the representation of value and reward processing in a variety of decision-making contexts (Levy & Glimcher, 2012; Liu et al., 2011). In a previous study utilising a version of this paradigm, the researchers reported that the vmPFC signal tracked both increasing favourable and decreasing unfavourable updates (Kuzmanovic et. al., 2015). The authors concluded that the region tracks the subjective affective meaning of judgements, independently of the valence of judged stimuli. Similarly, in the context of stimuli with positive and negative valences, the vmPFC activity

correlates with personal, self-reported ratings rather than with objective stimulus characteristics (Winecoff et al., 2013). We not only found activation in the vmPFC in response to social positive estimation errors (i.e. bad social events are less likely to happen), but also in response to social negative estimation errors (i.e. bad social events are more likely to happen). Thus, we could speculate that the higher vmPFC activity observed in HS subjects, compared to LS subjects, demonstrated a higher subjective affective value of social information in these samples. The higher vmPFC activity, in the context of stimuli with positive and negative valence, could represent higher internally modulated subjective values for social events. Indeed, activity in the vmPFC has been linked to processing social stimuli with a high degree of self-relevance (Northoff, Qin, & Nakao, 2010). The vmPFC also exhibits heightened responses during non-comparative judgments about self-similar (as opposed to dissimilar), unfamiliar social targets (Mitchell et al., 2005). Large scale meta-analysis of the PFC points to a broader role for the vmPFC in the generation of affective meaning, synthesizing social knowledge with emotions to create contextually appropriate models of the self (Roy & Pakala, 2012). Thus, there are findings to demonstrate that vmPFC concurrently tracks both personal relevance/value and self-similarity during social comparisons (Moore, Merchant, Kahn, & Pfeifer, 2014) and we speculate this is why the region was differentially active in HS subjects in response to estimation errors in social trials, regardless of valence, but not in non-social trials.

We not only found activation in the vmPFC in response to social positive estimation errors (i.e. bad social events are less likely to happen), but also in response to social negative estimation errors (i.e. bad social events are more likely to happen). Activity in the vmPFC has been linked to making judgments about the enduring characteristics of others (Van Overwalle, 2009), to explicit self-reflection (van der Meer, Costafreda, Aleman, & David, 2010) and to processing social stimuli with a high degree of self-relevance (Northoff, Qin, & Nakao, 2010).

The vmPFC also exhibits heightened responses during non-comparative judgments about self-similar (as opposed to dissimilar), unfamiliar social targets (Mitchell et al., 2005). Large scale meta-analysis of the PFC points to a broader role for the vmPFC in the generation of affective meaning, synthesizing social knowledge with emotions to create contextually appropriate models of the self (Roy & Pakala, 2012). Thus, there are findings to demonstrate that vmPFC concurrently tracks both personal relevance and self-similarity during social comparisons (Moore, Merchant, Kahn, & Pfeifer, 2014) and we speculate this is why the region was differentially active in HS subjects in response to estimation errors in social trials, regardless of valence, but not in non-social trials.

In addition, we found greater dlPFC activity in LS subjects compared to HS subjects in response to social positive estimation errors. This region has primarily been associated with executive functions (Mansouri, Tanaka, & Buckley, 2009) such as working memory, selective attention and certain forms of inhibition (Roberts, Robbins, & Weiskrantz, 1998; Tallent & Gooding, 1999). Further, tasks specifically designed to assess the representation and maintenance of context also elicit DLPFC activity (Barch et al., 1997; Cohen et al., 1994; Delawalla, Csernansky, & Barch, 2008; MacDonald & Carter, 2003; Sylvester et al., 2003). By maintaining a rich representation of the task context (for example, relevant rules or stimulus-response mappings), the DLPFC might support top-down control. The overall conclusion is that although the dorsolateral PFC is but one critical structure in a network of anterior and posterior "attention control" areas, it does have a unique executive attention role in actively maintaining access to stimulus representations and goals in interference-rich contexts (Kane & Engle, 2002). The finding of higher activity in this region in LS subjects, in comparison to HS subjects, in response to social positive errors might suggest that executive and inhibitory control is impaired in HS individuals and might suggest a problematic contextual representation for social events with good news. This interpretation would be in line with

findings that schizophrenia patients are impaired in contextual processing as characterised by lower dlPFC activity (Barch et al., 2001; Delawalla, Csernansky, & Barch, 2008; Holmes et al., 2005; MacDonald & Carter, 2003).

The current findings need to be considered in line with the limitations of the study. Due to scanning time constraints for the current project, we could only include 60 trials, with 15 events per interaction term. In comparison, previous work has generally included 88 trials with half being positive half negative (Garrett et al., 2014; Garrett & Sharot, 2017; Sharot et al., 2011; Sharot et al., 2012). While we did replicate the optimism bias observed in previous studies, the limited number of trials could have affected the power to detect group differences. However, we speculate the inclusion of more trials might not affect the behavioural results as the literature suggests HS cohorts present with behaviourally similar performance to LS in social tasks (Kozhuharova et al., 2020). Another limitation relates to the lack of assessment of subjectively experienced estimation errors. While formally the estimation error with this type of task corresponds to the difference between participants' first estimate and the presented base rate in each trial, the participants may not perceive this difference as an indication that their initial judgement was erroneous because of personal vulnerabilities. For instance, a strong family history of cancer may suggest a higher personal risk of suffering from cancer relative to the general population base rate, so that a presentation for a lower population base rate may not be subjectively perceived as an error. Subjective experience of estimation errors needs to be assessed to improve the methodological precision of the paradigm.

Despite these limitations, the current work presents a valuable contribution to the field. The current study benefits from a clearly defined LS vs HS cohort, where both groups present the extremes of the schizotypy continuum. With a modified version of the belief-updating task (Sharot et al., 2011; Sharot et al., 2014) we investigated the learning patterns associated with

social information and the neural network tracking prediction errors in this paradigm. Behavioral findings indicate that people not only update more in response to good news (optimism bias; Sharot et al., 2016), but they also update more in response to social events as compared to non-social events. While, as expected, we found no group differences in belief updating patterns in the current task, we found a broad range of altered neural activity in the HS subjects. Compared to LS subjects, HS subjects showed greater activity in the vmPFC and the left IFG, and lower activity in the dlPFC, in response to social prediction errors (both negative and positive interaction conditions). These findings suggest that, in order to achieve the same behavioural performance as LS subjects, the prefrontal cortex is over activated in HS individuals particularly during self- and other- referential processing. Furthermore, socially salient estimation errors might trigger a more substantial effort to integrate social information into prior beliefs, compared to non-social estimation errors. Lower activity in the dlPFC in HS subjects for tracking social positive errors might suggest a problematic contextual representation for social events with good news. Finally, across individual task conditions we observed a widespread network of lower functional activity in the HS subjects in response to prediction errors with main regions being the IFG, MFG and ventral striatum. These findings strongly suggest that high schizotypy is associated with a dysfunctional brain response during social prediction errors paralleling findings in schizophrenia patients.

Chapter Five

High schizotypy individuals present with impaired learning under volatility in social context

Abstract

Social cognition is particularly impaired in schizophrenia and, in clinical high risk for schizophrenia populations, it is a key predictor of illness outcome. Furthermore, aberrant learning under uncertainty has been shown to drive abnormal beliefs, including social learning deficits. To date however, this has not been tested in individuals with schizotypy traits, a known risk factor for the development of psychosis. We addressed this question by integrating a social probabilistic learning paradigm, functional magnetic resonance imaging (fMRI), and computational modelling in a sample of high schizotypy (HS) and low schizotypy individuals (LS) as defined by the extreme ends of the spectrum assessed using the Schizotypy Personality Questionnaire. We find that HS compared to LS participants show a reduced impact of volatility on advice-taking behaviour. Computational modelling of participants' choices suggests abnormal social learning in HS compared to LS participants: HS initially perceived intentions as more volatile and tended to stick to those beliefs, showing a reduced learning rate about volatility. The fMRI results were in line with those behavioral findings: In contrast to LS, HS participants showed an attenuated processing of outcome prediction errors in the midbrain and insula and enhanced effects of intention volatility in prefrontal regions. Taken together, the results suggest that HS participants show aberrant learning about environmental volatility, as reported in schizophrenia and clinical high-risk individuals.

5.1. Introduction

Schizophrenia is conceptualized as a chronic neurocognitive disorder that presents with diverse symptomology and heterogeneous levels of severity and functioning (Freedman et al., 2005; Ross, Margolis, Reading, Pletnikov, & Coyle, 2006). Despite available treatments, approximately two-thirds of affected individuals have fluctuating and recurring symptoms throughout their life and available antipsychotic medications do not effectively alleviate deficits in cognitive and social functioning (Carrion et al., 2013; Saha, Chant, Welham, & McGrath, 2005). This diversity of clinical trajectories and treatment responses across patients calls for new approaches to dissect the schizophrenia spectrum into subgroups or dimensions (Stephan, Friston, & Frith, 2009). Two potential avenues to pinpointing meaningful dimensions are the use of mathematical (computational) models to investigate behaviour and neural activity (Adams, Huys, & Roiser, 2016; Stephan, Iglesias, Heinzle, & Diaconescu, 2015) and their applications in the context of clinical high risk populations for early detection and prevention of psychosis (Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009).

The earliest cohort conceded to represent an underlying vulnerability for schizophrenia includes healthy individuals in the general population scoring high on schizotypal personality traits (Ettinger, Meyhofer, Steffens, Wagner, & Koutsouleris, 2014; Meehl, 1990; Nelson, Seal, Pantelis, & Phillips, 2013; Raine, 1991). The rate of high schizotypy (HS) individuals meeting criteria for a schizophrenia-spectrum diagnosis at a 10-year follow-up assessment is estimated to be around 2% (Kwapil, Gross, Silvia, & Barrantes-Vidal, 2013; Van Os et al., 2009) and epidemiologic and clinical studies have supported a symptomatic continuum of psychotic-like experiences (e.g. delusional and hallucinatory) within these populations (Krabbendam, Myin-Germeys, Bak, & Van Os, 2005; Livingston, Kitchen, Manela, Katona, & Copeland, 2001; Lundberg, Cantor-Graae, Kabakyenga, Rukundo, & Östergren, 2004; Wiles et al., 2006).

Research has consistently demonstrated similarities between schizotypy and schizophrenia with parallel, albeit attenuated symptoms and deficits in (social) cognition and perception (Ettinger, et al., 2014; Phillips & Seidman, 2008). Similar neural abnormalities have also been observed between schizotypy and schizophrenia patients, with both anatomical (Ettinger et al., 2012; Kühn, Schubert, & Gallinat, 2012; Raine, Sheard, Reynolds, & Lencz, 1992) and functional investigations (Corlett & Fletcher, 2012; Ettinger et al., 2014; Meyhöfer et al., 2015) showing alterations relative to control groups. Thus, assessment of schizotypy individuals may facilitate the study of vulnerability and risk markers for the illness as well as potential developmental pathways to psychosis.

A crucial area of research for developmental trajectories to psychosis are the social cognition deficits characteristic of schizophrenia-spectrum conditions, because poor social functioning is linked to a lower quality of life (Penn, Corrigan, Bentall, Racenstein, & Newman, 1997) and predicts illness outcome in schizophrenia, including relapse, poor illness course and unemployment (Álvarez-Jiménez et al., 2012; Brune, Schaub, Juckel, & Langdon, 2011; Couture, Penn, & Roberts, 2006; Kring & Elis, 2013). Individuals with schizophrenia often display marked impairments in processing social information, which can result in misinterpretations of the social intent of others and delusional beliefs, social withdrawal and impaired daily social functioning (Fett, Viechtbauer, Penn, van Os, & Krabbendam, 2011; Green, Hellemann, Horan, Lee, & Wynn, 2012). Indeed, in such individuals, social cognitive impairment has a more negative effect on daily functioning than non-social cognitive impairments (Fett et al., 2011; Green et al., 2012). Patients with schizophrenia show widespread impairment in the processing of social information, particularly when processing emotional stimuli and when inferring the intentions of others (Green, Horan, & Lee, 2015; Penn, Sanna, & Roberts, 2008; Pinkham, 2014; Sprong, Schothorst, Vos, Hox, & Van Engeland, 2007; Ventura, Wood, Jimenez, & Hellemann, 2013).

Neural regions implicated in social cognition, including the medial prefrontal cortex (mPFC), ventromedial PFC (vmPFC), inferior frontal gyrus (IFG) and superior frontal gyrus (SFG), show both increased and decreased patterns of activation in both schizotypy populations (Healey, Morgan, Musselman, Olino, & Forbes, 2014; Modinos, Renken, Shamay-Tsoory, Ormel, & Aleman, 2010; Modinos, Ormel, & Aleman, 2010; Modinos, Renken, Ormel, & Aleman, 2011; Mohanty et al., 2005; Wang, Ettinger, Meindl, & Chan, 2018) and in clinical high risk for schizophrenia populations (Modinos et al., 2015; Modinos, Allen, Grace, & McGuire, 2015; Pelletier-Baldelli, Orr, Bernard, & Mittal, 2018; Seiferth et al., 2008; Stanfield et al., 2017; Wolf et al., 2015). Neuroimaging studies have implicated regions in the prefrontal cortex (PFC) in inferring on the internal states and intentions of others, in regulating emotion, in processing reward and punishment and in the contextual interpretation of complex social information (Phan, Wager, Taylor, & Liberzon, 2002). The consistent patterns of altered activity in these regions in at-risk and clinical populations during social cognition tasks might represent abnormal processing of socially salient cues leading to aberrant beliefs about others and thus contributing to the formation of delusions (Corlett, Taylor, Wang, Fletcher, & Krystal, 2010; Morrison, Renton, Dunn, Williams, & Bentall, 2004).

Despite studies consistently reporting an abnormal neural response to social cues in schizotypy samples (particularly increased activity in frontal regions; (Kozhuharova, Saviola, Ettinger, & Allen, 2020), they also report a lack of behavioural differences on these tasks between HS and low schizotypy (LS) individuals. This is in contrast with findings from clinical high risk, where individuals present with Theory of Mind (ToM), social perception/cognition and facial affect recognition impairments alongside similar abnormal neural responses (Addington, Penn, Woods, Addington, & Perkins, 2008; Kozhuharova et al., 2020; Piskulic et al., 2016; Thompson, Bartholomeusz, & Yung, 2011; Van Donkersgoed, Wunderink, Nieboer, Aleman, & Pijnenborg, 2015). Thus, it is unclear what is driving the abnormal neural activity

associated with normal behavioural performance during social cognition in HS and what this signifies for psychosis progression risk. Computational accounts of the cognitive and neural processes underlying the earliest risk states may be highly beneficial to offer insight into the mechanisms driving learning from socially salient cues (i.e. how prediction errors and uncertainty estimation influence learning from social information).

Computational frameworks, mainly hierarchical Bayesian inference models, play a prominent role in theories of schizophrenia (Adams, Stephan, Brown, Frith, & Friston, 2013; Corlett, Frith, & Fletcher, 2009; Corlett et al., 2010; Stephan, Penny, Daunizeau, Moran, & Friston, 2009). The central nation is that the brain instantiates a generative model of its sensory inputs, i.e., a model that makes predictions about the environment and how its (hidden) states give rise to sensations. Perceptual inference rests on inverting the model to determine the most likely cause of sensory input; learning serves to update beliefs such that future sensory inputs can be better predicted. Importantly, under very general assumptions, these belief updates have a generic form: they are proportional to prediction errors (PEs), weighted by a precision ratio that serves as a dynamic learning rate and balances the expected precision of low-level (e.g., sensory) input against the precision of prior beliefs (see Eqs. (1) and (2); see also Mathys et al., 2014). This is motivated by the putative relation of outcome-related PEs to phasic dopamine (DA) release and its possible involvement in aberrant learning in schizophrenia (Adams et al., 2013; Corlett et al., 2007; Corlett et al., 2009; Corlett et al., 2010; Ermakova et al., 2018; Gradin et al., 2011; Murray et al., 2008; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006; Schultz, Dayan, & Montague, 1997). The dopaminergic PE signal is thought to represent a neural response to deviation from an expected outcome (of rewards but also sensory features; (Gardner, Schoenbaum, & Gershman, 2018; Iglesias et al., 2013; Suarez, Howard, Schoenbaum, & Kahnt, 2019) and likely supports the updating of beliefs about the environment. The corollary from this general update rule is that unusually pronounced belief

updates can arise from two sources: by assigning too much precision to sensory inputs, or by developing overly uncertain prior beliefs.

Here we investigated these putative mechanisms of aberrant social learning and decision-making under environmental uncertainty (volatility) by examining advice-taking behaviour and brain activity of individuals scoring at the extreme ends of the schizotypy dimension. To this end, we combined fMRI using a probabilistic learning task (under conditions of volatility) with computational modelling, by employing the hierarchical Gaussian filter (HGF). This computational model of behaviour emphasises the importance of uncertainty for updating a hierarchy of beliefs via precision-weighted PE signals (Mathys et al., 2014; Mathys, Daunizeau, Friston, & Stephan, 2011). Furthermore, our task focused on learning from both social and non-social cues to investigate how a personality trait that increases risk for psychosis impacts social learning. We predict that, in line with previous work in clinical high risk (Cole et al., 2020), HS individuals will present with atypical learning under uncertainty that will impact advice-taking behaviour.

5.2. Methods

5.2.1. Participants

A total of 1342 participants responded to an online survey advertised via social media and were pre-screened using the Schizotypy Personality Questionnaire (SPQ; Raine, 1991) and the Marlowe-Crowne Social Desirability Scale (SDS; Fischer & Fick, 1993). All participants that took part in the MRI study were recruited from the student population of the Royal Holloway University of London. Exclusion criteria was defined as presence of contraindicators for MRI scanning (presence of metal, etc.), current use of prescribed medication for neuropsychiatric disorders or history of neuropsychiatric disorders, current use or history of

illicit substances misuse. These criteria were assessed via self-report and pre-screening for MRI scanning. The SDS questionnaire was used to exclude participants that give mainly socially desirable answers, thus only individuals scoring 8 or higher on this measure were excluded to control for socially desirable responding (Fischer & Fick, 1993).

Participants were invited to take part in the study based on their SPQ score. The aim of the study was to recruit the bottom and top 10% (decilles) of the schizotypy continuum (SPQ distribution). Thus, individuals scoring below 12 and above 41 points on the SPQ were invited to take part (as informed by previous research; Raine, 1991). The SPQ provides an overall measure of individual differences in schizotypal personality traits and can be reduced to three latent dimensions (positive, disorganised and negative; (Raine et al., 1994), mimicking the symptom clusters of schizophrenia and clinical high-risk states. The final sample included 27 participants in the high schizotypy group (HS; 17 females, age range 18-22, M = 19.25, SD = 1.05) and 26 participants in the low schizotypy group (LS; 19 females, age range 18-27, M = 20.38, SD = 2.02).

Ethical approval for the study was obtained from the University of Roehampton's Ethics Committee and all participants provided informed written consent before initiating any study procedures. Participants were compensated for their time (£40 cash payment and a high-resolution anatomical scan of their brain).

5.2.2. Behavioural assessments

On the day of MRI scanning participants completed a validated short version of the Wechsler abbreviated scale of intelligence (WASI II; McCrimmon & Smith, 2013) to assess intellectual ability. Working memory was assessed using the digit span backward task (Dobbs & Rule, 1989). Analysis of demographic and questionnaire data with the effect of group being

tested using chi square test or independent samples t-test for parametric data (significance threshold $p < .05$) was performed in R.

5.2.3. Experimental paradigm

The experimental paradigm used in our study was based on previous computational studies assessing individual differences in social cognition (Sevgi, Diaconescu, Henco, Tittgemeyer, & Schilbach, 2020). The game consisted of card and advice cues with varying winning probabilities. The advice cue (hand pointing to either card presented in the centre of the screen, Fig. 1A) was manipulated to change during each trial and to be pointing towards one of the cards before participants were allowed to make their choice. As a result, two things needed to be learned simultaneously during the task: first, whether the reward (points gained) is associated with the white or the purple card; and second, whether the advice cue is directed towards the card that is winning. Both the card probability (winning card colour) and the advice accuracy probability (probability that the advice cue points to the winning card on that particular trial) were systematically varied in accordance with a probabilistic schedule and were assorted independently of each other throughout the task (Fig 1B). The phases in which the trials have cues with unstable accuracy are referred to as volatile phases. In the first half of the experiment (trials 1-60), card accuracy was stable and high, whereas in the second half (trials 60-120), it followed a volatile phase. For the advice cue accuracy, the volatile phase took place between trials 50-120. Positions of the cards (left or right) were determined randomly.

In the instructions, participants were informed about the cards' having winning probabilities, which could change during the experiment. On each trial, there would be only one correct card, and by choosing the correct card participants gained a point. Participants were instructed that choosing the wrong card or not providing a response would cost them a point.

They were instructed they will receive feedback from another player in the form of a hand. Participants' goal was to get as many points as possible throughout the task, and they were also instructed that the other player might have different incentives and different goals, similar to other paradigms using explicit advice (Diaconescu et al., 2014). The task was presented and recorded via PsychoPy2 (Python-based, Peirce et al., 2019). At the end of the study, all participants were asked about the strategies they had employed during the game and about the other player's strategy to verify whether participants truly believed they were playing with another person.

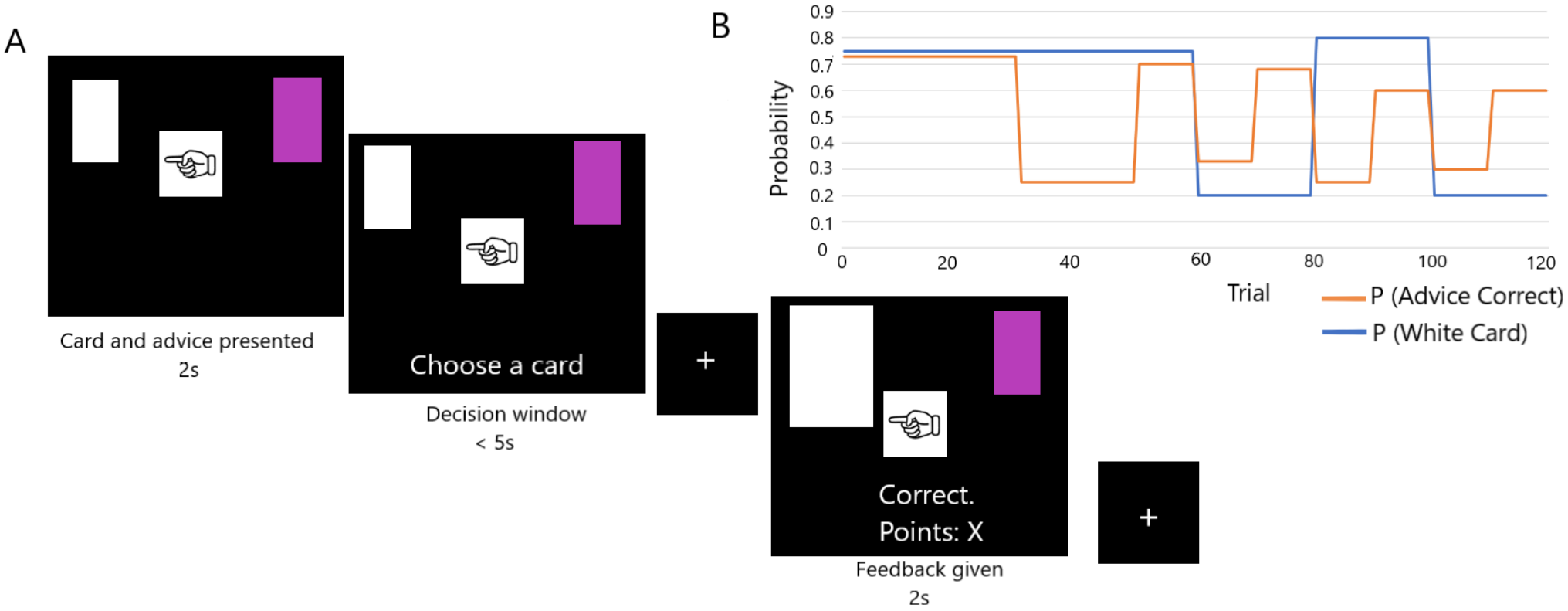

Fig 1. The experimental design. (A) Participants are presented with the card and advice for 2s, then they have up to 5s to make a decision (i.e. choose a card). There is an intermittent fixation cross, which corresponds to the time left of the decision window (if a participant responds in 2s, the intermittent fixation cross is 3s). Participants are presented with feedback for 2s. During feedback, the card chosen by the participants gets bigger, they are told if their choice was correct or incorrect and how many points they have at this moment in the game. The end of trial fixation cross is jittered 1-4s. (B) the probabilities associated with the cues in the task (consistent across the whole sample), blue line represents probability of white card winning (i.e. card accuracy), orange line represents the probability of the advice being correct (i.e. advice accuracy).

5.2.4. Behavioural Modelling

The computational framework adopted in this study was guided by Bayesian theories of brain function that suggest that the brain maintains and continuously updates a generative model of its sensory inputs (Dayan, Hinton, Neal, & Zemel, 1995; Friston, 2005; Rao & Ballard, 1999). Individuals are assumed to update their beliefs about states of the external world based on the sensory inputs they receive (perceptual model); these beliefs, in turn, provide a foundation for making decisions (response model; (Daunizeau et al., 2010). An application of this approach is a generative model called the Hierarchical Gaussian Filter (HGF), which accounts for deterministic and probabilistic relationships between the environment and perceptual states (Mathys et al., 2011).

We used a perceptual-response model combination to infer on participants' predictions about the task outcomes. This approach allowed the estimation of hierarchically coupled hidden states that describe participants' learning about the environmental statistics, namely, the probability and the volatility of the card and the advice cues, based on their responses. These subjective beliefs are weighted by their precision to form the basis of a response model (of the observed behaviour) as explained in detail below. The graphical representation of the perceptual model is shown in Fig 2.

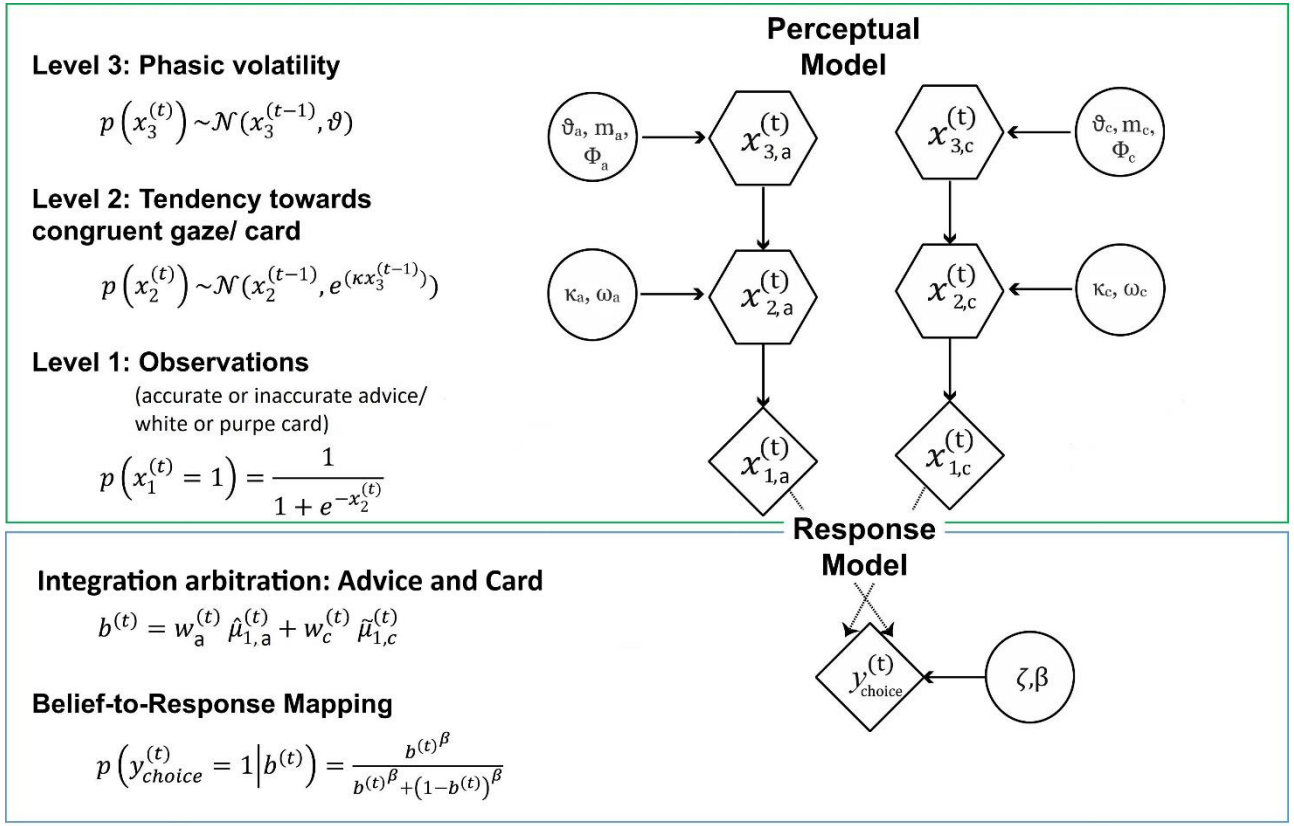

Fig 2. Graphical representation of the winning model combination: "mean-reverting HGF" perceptual model and the "volatility" response model. The graphical representation depicts two parallel learning systems, circles represent constants and diamonds represent quantities that change in time (i.e. that carry a time/trial index). Hexagons, like diamonds, represent quantities that change in time, but additionally depend on the previous state in time in a Markovian fashion. The letter a refers to the HGF for advice cues, the letter c refers to the HGF for the card cues. x1 represents the cue probability (card or advice, respectively), x2 the cue-outcome contingency and x3 the volatility of the cue-outcome contingency. Parameter κ determines how strongly x2 and x3 are coupled, ω determines log-volatility or tonic component of x2, ϑ represents the volatility of x3, and m represents the mean of the drift towards which x3 regresses to in time. The response model parameter β represents the inverse decision temperature and determines the belief-to-response mapping.

5.2.5. Perceptual model: Hierarchical Gaussian Filter

The HGF is a hierarchical model of learning, which allows for inference on an agent's beliefs (and their uncertainty) about the state of the world from observed behaviour (Mathys et al., 2011) and has been used by several recent behavioural and neuroimaging studies on different forms of learning (De Berker et al., 2016; Diaconescu et al., 2014; Hauser et al., 2014; Lawson, Mathys, & Rees, 2017; Powers, Mathys, & Corlett, 2017; Siegel, Mathys, Rutledge, & Crockett, 2018; Vossel et al., 2014). The model proposes that agents infer on the causes of sensory inputs using hierarchically-coupled belief updates that evolve in time as Gaussian random walks where, at any given level, the variance (step size) is controlled by the state of the next higher level (Mathys et al., 2011; Mathys et al., 2014). A standard formulation of the HGF for standard binary decision-making tasks includes three levels, where the first (lowest) level encodes the probability of a trial outcome. Here, it denotes whether the correct card colour was selected or not; and whether the advice was accurate or not. The 2nd level represents the tendency of the winning card colour or the adviser fidelity as continuous quantities, and the 3rd level represents the volatility of this tendency (Fig 2; Mathys et al., 2011).

In this study, we included two parallel HGF learning systems, consistent with recent studies using similar experimental paradigms (see Fig 2; Diaconescu et al., 2020; Henco et al., 2020). The following subject-specific parameters determine how the above states at each time point t evolve in time: (i) κ determines the degree of coupling between the second and third level in the hierarchy ($x_2^{(t)}$ and $x_3^{(t)}$) and the degree to which the volatility influences the tendency of the winning card colour and the adviser's fidelity; (ii) ω represents the evolution rate at the second level or the baseline component of the log-volatility of $x_2^{(t)}$, capturing the subject-specific magnitude of the belief update about the stimulus-outcome probabilities that

is independent of $x_3^{(t)}$; (iii) ϑ represents the meta-volatility parameter (the evolution rate of $x_3^{(t)}$), or how rapidly the volatility of the associations changes in time. Furthermore, we also estimated $\mu_3^{(t=0)}$, the subject's initial belief about environmental volatility.

A key notion of the HGF is that subjects update their beliefs about hierarchically-coupled states in the external world by using a variational approximation to intractable full Bayesian inference (Mathys et al., 2011). The update rules that emerge from this approximation have a structural form similar to RW reinforcement learning, but with a dynamic (adaptive) learning rate determined by the next-higher level in the hierarchy. Formally, at each hierarchical level i, predictions (posterior means $\mu_i^{(t)}$) on each trial t are proportional to precision-weighted PEs, $\varepsilon_i^{(t)}$ (Eqs. (1) and (2)). The general form of this belief update (with subtle differences for categorical quantities at the lowest level) is the product of the PE from the level below $\delta_{i-1}^{(t)}$, weighted by a precision ratio $\varphi_i^{(t)}$:

$$\Delta\mu_i^{(t)} \propto \varphi_i^{(t)}\, \delta_{i-1}^{(t)} \tag{1}$$

$$\text{where } \varphi_i^{(t)} = \frac{\hat{\pi}_{i-1}^{(t)}}{\hat{\pi}_i^{(t)}} \tag{2}$$

Here, $\hat{\pi}_{i-1}^{(t)}$ and $\hat{\pi}_i^{(t)}$ represent estimates of the precision of the prediction about input from the level below (e.g., precision of sensory data) and of the prediction at the current level, respectively (for details, see (Mathys et al., 2011). This precision-weighting is critical for adaptive learning and emerges naturally from hierarchical Bayesian formulations (Adams et al., 2013; Corlett et al., 2010; Friston, 2008; Iglesias et al., 2013; Mathys et al., 2011). Simply speaking, PEs have a larger weight (and thus updates are more pronounced) when the precision of the data (input from the lower level) is high, relative to the precision of prior beliefs.

The belief precision weighting the PE depends on the estimated environmental volatility and the low-level (sensory) precision:

$$\pi_{2,a}^{(t)} = \hat{\pi}_{2,a}^{(t)} + \hat{\mu}_{1,a}^{(t)}(1 - \hat{\mu}_{1,a}^{(t)}), \quad \pi_{2,c}^{(t)} = \hat{\pi}_{2,c}^{(t)} + \hat{\mu}_{1,c}^{(t)}\left(1 - \hat{\mu}_{1,c}^{(t)}\right) \tag{3}$$

with the precision of the prediction given by:

$$\hat{\pi}_{2,a}^{(t)} = \frac{1}{1/\pi_{2,a}^{(t-1)} + \exp\left(k_a \mu_{3,a}^{(t-1)}\right)} \quad , \hat{\pi}_{2,c}^{(t)} = \frac{1}{1/\pi_{2,c}^{(t-1)} + \exp\left(k_c \mu_{3,c}^{(t-1)}\right)}$$

(4)

where $\mu_3^{(t-1)}$ is the predicted environmental volatility.

5.2.6. Mean-reverting HGF

The standard HGF, described above, already allows for representing (and inferring) the precision of low-level PEs and prior beliefs and thus offers the two components required to test our hypothesis. We can finesse this model further by using a variation of the classical HGF that allows for inferring on drifts in an agent's beliefs. In other words, we assume that participants' beliefs do not only vary as a function of precision-weighted PEs but may also drift towards an equilibrium point m_3 (essentially the equivalent of an Ornstein-Uhlenbeck process in discrete time; Doob, 1942). Here, we used this model to examine the hypothesis that HS compared to LS participants might show a tendency to overestimate the volatility of the environment, which would further enhance the weight (precision) of low-level PEs and lead to an inflation of uncertainty about probabilities over time. As described above, a scenario of this sort may lead to later compensation, for example by, adopting high-order beliefs with inappropriately high precision and may thus represent a risk factor for delusion formation.

The equations describing the generative model are summarised in Fig. 2. Notably, the third level of this model includes subject-specific parameters that represent the agent's individual starting estimate of volatility, $\mu_3^{(t=0)}$, as well as the equilibrium point m_3, which the agent's estimate of volatility drifts towards (Fig. 3). The prior on m_3 was equivalent to the prior on $\mu_3^{(t=0)}$; hence the model did not include any prior assumption about the direction of the equilibrium point relative to the starting value of the volatility estimation.

5.2.7. Precision Weighted Response Model

We applied this model to derive subject-specific accuracy and volatility estimates for card and advice in a parallel manner. On a given trial t, subjects generated a combined belief, $b^{(t)}$, after weighting the posterior expectation of inferred card and advice accuracies, $\hat{\mu}_{1,c}^{(t)}$ and $\hat{\mu}_{1,a}^{(t)}$, to generate actions in the following manner:

$$w_a^{(t)} = \frac{\zeta\hat{\pi}_{1,a}^{(t)}}{\zeta\hat{\pi}_{1,a}^{(t)}+\hat{\pi}_{1,c}^{(t)}}, \qquad w_c^{(t)} = \frac{\hat{\pi}_{1,c}^{(t)}}{\zeta\hat{\pi}_{1,a}^{(t)}+\hat{\pi}_{1,c}^{(t)}} \tag{5}$$

$$b^{(t)} = w_a^{(t)}\,\hat{\mu}_{1,a}^{(t)} + w_c^{(t)}\,\tilde{\mu}_{1,c}^{(t)}, \tag{6}$$

where $w_a^{(t)}$ and $w_c^{(t)}$ are effective precision ratios of advice and card cues, $\hat{\mu}_{1,c}^{(t)}$ is the transformed expected card colour probability from the perspective of the advice (i.e., the estimated card colour probability indicated by the hand), and $\hat{\mu}_{1,a}^{(t)}$ corresponds to the logistic sigmoid of the current expectation of advisor fidelity:

$$\hat{\mu}_{1,a}^{(t)} = s\,(\mu_{2,a}^{(t-1)}) = \frac{1}{1+\exp\,(-\mu_{2,a}^{(t-1)})} \tag{7}$$

Response model parameter ζ is the weight on the precision of inferred advice accuracy or the additional bias toward the social cue; $\hat{\pi}_{1,a}^{(t)}$ and $\hat{\pi}_{1,c}^{(t)}$ are precisions (inverse variances) at the first level for advice and card accuracies, respectively. As the first level estimates are assumed to follow a Bernoulli distribution, one can calculate the precision at each trial by:

$$\hat{\pi}_{1,a}^{(t)} = \frac{1}{\hat{\mu}_{1,a}^{(t)}\,(1-\hat{\mu}_{1,a}^{(t)})}, \quad \hat{\pi}_{1,c}^{(t)} = \frac{1}{\hat{\mu}_{1,c}^{(t)}\,(1-\tilde{\mu}_{1,c}^{(t)})} \tag{8}$$

The probability of taking the hand advice was assumed to be reflected by a softmax function:

$$p\,(y^{(t)} = 1|b^{(t)} = \frac{b^{(t)^{\beta}}}{b^{(t)^{\beta}} + \left(1-b^{(t)}\right)^{\beta}} \tag{9}$$

where β > 0 is the subject-specific inverse decision temperature parameter. A low decision temperature (high β) means often selecting the highest probability colour, whereas a high decision temperature (low β) means sampling randomly from a uniform distribution.

5.2.8. Bayesian model selection and computational regressors

Several different hypotheses about how participants inferred on the probabilistic stimulus-outcome contingencies were embodied in the following model space (Fig 3A). Regarding the perceptual model, our main question was whether participants' predictions about reward probabilities based on stimulus-outcome associations had a hierarchical structure and accounted also for the volatility of these associations. We thus compared (i) a non-hierarchical model, based on a reduced Hierarchical Gaussian Filter (HGF) that assumes that subjects do not infer on the volatility of stimulus-outcome probabilities (M_1 , M_6 ;

see Diaconescu et al., 2014), (ii) a three-level HGF (M_2 , M_7 ; see Mathys et al., 2011) and (iii) a mean-reverting HGF in which volatility estimates drift towards a subject-specific equilibrium (M_3 , M_4, M_5 , M_8 , M_9 , M_{10} ; see Cole et al., 2020). With respect to the response model, we followed previous work (Diaconescu et al., 2014) and considered two possible mechanisms of how beliefs were translated into responses (Fig 3A). Subjects choices could either be affected by card cue alone ("Card only" model family, $M_{1\text{-}5}$) or by both advice and card cue ("Arbitrated" model family, $M_{6\text{-}10}$). We assumed that participants' choices were either entirely affected by the estimated reward probabilities ("Reward" model family; $M_{1\text{-}5}$) or the integration between the advice and reward probability estimates ("Integrated" model family; $M_{6\text{-}10}$). Table 1 contains information on the prior means and variances used for these models. Please note that whereas the prior variances for all parameters are set to be rather broad, we selected a shrinkage prior mean and variance for the decision noise parameter β to ensure that behaviour is explained more by variations in the learning parameters rather than decision noise.

Table 1. Prior mean and variance of the model space included in this study.

Models and parameters	**Prior mean**		**Prior variance**	
(i) 2-level no-volatility HGF model class, M_1, M_6	**card**	**advice**	**card**	**advice**
κ	0	0	0	0
ω	-4	-4	16	16
ϑ	0.25	0.25	0	0
$\mu_2^{(t=0)}$	0	0	0	0
$\sigma_2^{(t=0)}$	log (1)	0	log (1)	0
$\mu_3^{(t=0)}$	1	1	0	0
$\sigma_3^{(t=0)}$	log (1)	0	log (1)	0
(ii) 3-level HGF model class, M_2, M_7				
κ	0.25	0.25	0	0
ω	-4	-4	16	16
ϑ	0.25	0.25	1	1

$\mu_2^{(t=0)}$	0	0	0	0
$\sigma_2^{(t=0)}$	log (1)	0	log (1)	0
$\mu_3^{(t=0)}$	1	1	1	1
$\sigma_3^{(t=0)}$	log (1)	0	log (1)	0
(iii) Mean-reverting HGF model class, *M*$_3$, *M*$_4$, *M*$_5$, *M*$_8$, *M*$_9$, *M*$_{10}$ (common parameter values across the class)				
ω	-5	-5	16	16
ϑ	0.5	0.5	1	1
$\mu_2^{(t=0)}$	0	0	0	0
$\sigma_2^{(t=0)}$	log (1)	0	log (1)	0
$\mu_3^{(t=0)}$	1	1	1	1
$\sigma_3^{(t=0)}$	log (1)	0	log (1)	0
***M*$_3$, M$_8$**				
κ	0.5	0.5	0	0
m_3	$\mu_3^{(t=0)}$	$\mu_3^{(t=0)}$	0	0
***M*$_4$, M$_9$**				
κ	0.5	0.5	1	1
m_3	$\mu_3^{(t=0)}$	$\mu_3^{(t=0)}$	1	1
***M*$_5$, M$_{10}$**				
κ	0.5	0.5	1	1
m_3	$\mu_3^{(t=0)}$	$\mu_3^{(t=0)}$	0	0
Response Model Parameters M$_1$, M$_2$, M$_3$, M$_4$, M$_5$				
β	48		1	
ζ	0		0	
Response Model Parameters M$_6$, M$_7$, M$_8$, M$_9$, M$_{10}$				
β	48		1	
ζ	1		25	

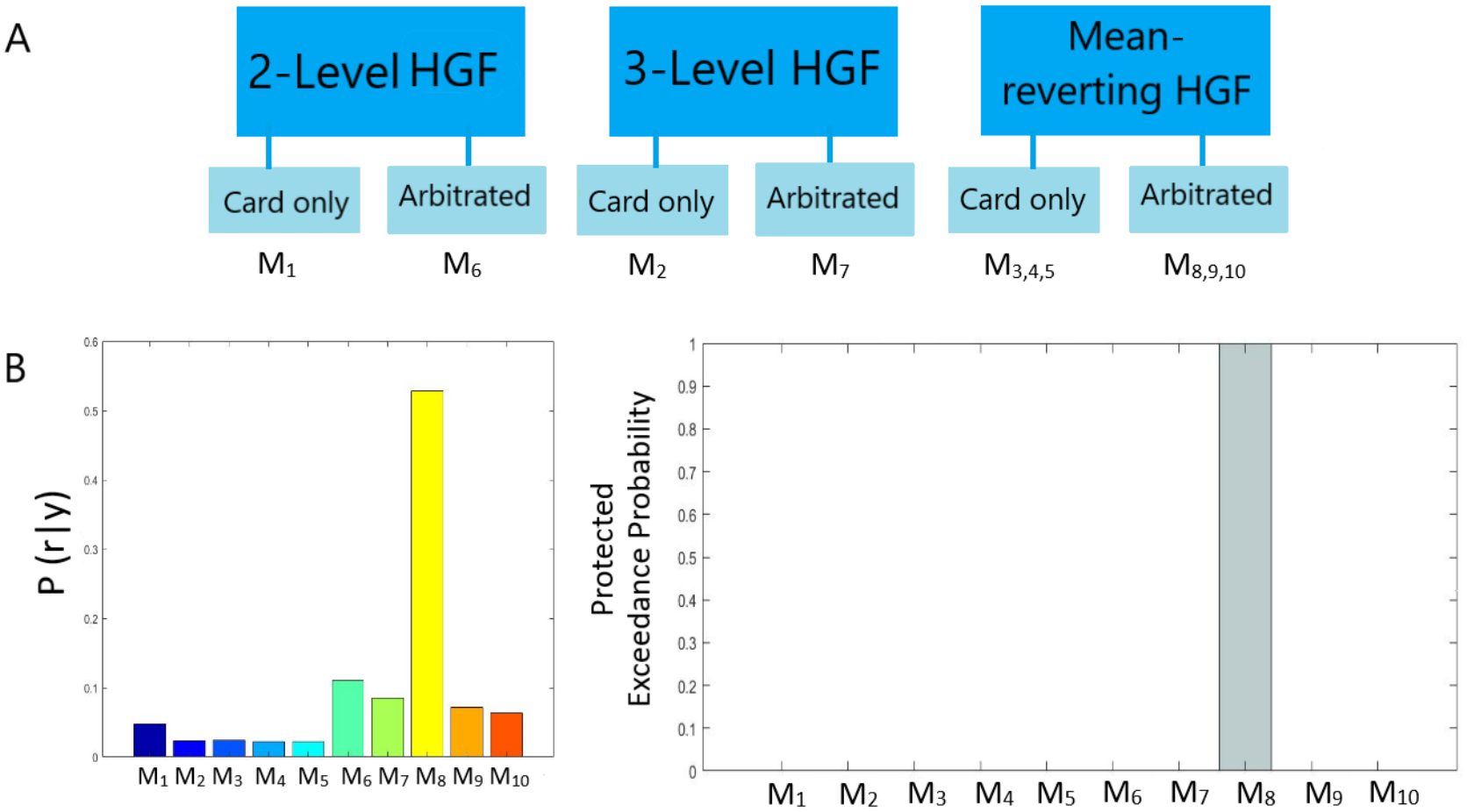

Fig 3. Hierarchical structure of the model space: perceptual models, response models and Bayesian model selection. (A) The models considered in this study have a factorial structure that can be displayed as a tree: The nodes at the first level represent the perceptual model families (2-level non-volatility HGF, 3-level HGF, and 3-level mean-reverting). The nodes at the second level represent the individual models. Two response model families were formalized under the HGF models: the mapping of beliefs-to-decisions either (i) relied only on the card cue ("Card only" model) or (ii) arbitrated between card and advice cues ("Arbitrated" model). (B) Bayesian model selection (BMS) reveals M_8, the mean-reverting HGF perceptual model in combination with the "Volatility" decision model, to best explain the data.

We compared the full set of resulting models $M_{1\text{-}10}$ using Bayesian model selection (Stephan et al., 2009), to determine which combination of perceptual and response models best explained the behavioural dataset and would thus optimally inform the subsequent analysis of fMRI data. Based on the model space outlined above (Fig. 3A), a total of ten different models were compared.

From the winning model (Fig. 3B), we performed perceptual parameter estimation using 10 sets of simulations per subject. Simulated responses were generated from each subject's corresponding perceptual parameters (for both advice and card probabilities). The purpose of the simulations was to test whether the parameter values that were estimated could also be recovered. Parameter recovery revealed significant correlations between original subject parameters and those estimated from simulations for all advice perceptual parameters in M_7 and for the response model parameters (Table 2). To compare recovery performance across parameters, we quantified it in terms of effect sizes, i.e., whether the correlation between the original and the recovered values indicates small, medium, large effect sizes. For a multiple regression, a Cohen's *f* above 0.4 is conventionally regarded as a large effect size.

Table 2. Correlations between original subject parameters and those estimated from simulations for all advice perceptual parameters and response parameters.

Parameter	Correlation	P-value	Effect size (Cohens *f*)
$\mu_{3,a}$	0.4	0.003	0.44
ω_a	0.42	0.002	0.46
ϑ_a	0.38	0.005	0.41
β	0.05	< 0.001	1.51
ζ	0.05	< 0.001	0.03

For the parameters that were recoverable (i.e. the parameters relating to advice), we extracted the trajectories of several trial-wise computational quantities, estimated for each

subject individually: (i) the prediction about the next outcome, (ii) uncertainty (Bernoulli variance) about the probability of the next outcome ('1st-level uncertainty'), (iii) their belief about the current volatility of the environment ($\hat{\mu}_3^{(t)}$), (iv) the predicted environmental uncertainty about the advice ($w_2^{(t)}$), (v) the absolute precision-weighted PE regarding the outcome on a given trial relative to their current beliefs about the probability of that outcome ($\varepsilon_2^{(t)}$), (vi) their belief uncertainty ('2nd-level uncertainty'; σ_2) and (vii) their signed precision-weighted PE regarding the perceived volatility of the outcome on a given trial relative to their current belief about that volatility ($\varepsilon_3^{(t)}$). Each of these trajectories was then used as a regressor (parametric modulator) in the single-subject fMRI analyses described below (Section 2.12).

5.2.9. Behavioural analysis

We subjected the MAP estimates of the recoverable perceptual and response parameters of the winning model to one-way analysis of covariance (ANCOVA) assessments, in order to test for differences in decision and learning parameters between HS and LS subjects. We included cognitive-perceptual (CP, equivalent to positive schizophrenia symptoms) SPQ factor as a covariate, in order to identify group differences independent of positive/paranoid symptoms. Previous work has associated positive/paranoid symptoms with differences in learning from uncertainty and volatility priors (Corlett et al., 2010; Diaconescu, Hauke, & Borgwardt, 2019; Fletcher & Frith, 2009; Reed et al., 2020); thus we included this covariate to remove this bias from affecting the results. To examine group differences in perceived (predicted) volatility induced by basic reversals of probabilistic contingency, we also performed a 2 (group: HS:LS, between subjects) × 2 (phase: stable, volatile, within subjects) mixed-factor ANCOVA (CP as a covariate) to examine group-by-phase interaction effects on

$\hat{\mu}_3^{(t)}$ (see the phases outlined in Fig 1). Additionally, we performed equivalent ANCOVAs for $\hat{\mu}_1^{(t)}$, $\varepsilon_2^{(t)}$ and $\varepsilon_3^{(t)}$ for the advice. Please note that the inclusion of CP as a covariate did not violate ANCOVA homogeneity assumptions across all of the aforementioned parameters (all Levene's test p values were > 0.05).

5.2.10. Image acquisition

Scanning was performed on a 3T Siemens Magnetom TIM Trio scanner using a 32-channel head coil at the Combined Universities Brain Imaging Centre. A structural scan was acquired for co-registration of the EPI data by means of a weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MP Rage; repetition time 1900s; 1mm x 1mm x 1mm voxel size; in plane resolution of 256 x 256 x 176 slices, scanning time approximately 5 minutes). FMRI data during the experimental paradigm were acquired in two sessions with a T2*-weighted gradient echo planar imaging sequence (repetition time: 2s , echo time: 30ms, flip angle: 78° , 2.5 x 2.5 x 2.5 voxel size, 204mm field of view, 80 x 80 matrix size, 52 axial sections collected with multiband interleaved ascending acquisition, parallel in-plane reduction factor of 2). Stimuli and response displays were projected onto a screen at the end of the magnet bore that participants viewed via a mirror mounted on the head coil.

5.2.11. fMRI preprocessing

Data was preprocessed following the recommended pipeline for the analysis of Connectomes (C-PAC; Craddock et al., 2013). The anatomical image was deobliqued using 3drefit in the Analysis of Functional NeuroImages (AFNI) framework (https://afni.nimh.nih.gov) and reoriented into RPI using AFNI's 3dresample. Skull stripping

was performed with FSL BET (Smith, 2002). FSL FLIRT was used to perform a linear transformation of the skull stripped image into 2mm Montreal Neurological Institute (MNI) template space (Jenkinson, Bannister, Brady, & Smith, 2002). The registration was then refined using non-linear transformation performed by FSL FNIRT (Andersson, Jenkinson, & Smith, 2007). The skull stripped normalised T1 was segmented using FSL FAST (Zhang, Brady, & Smith, 2001). Tissue masks for the cerebrospinal fluid (CSF), white matter (WM) and grey matter (GM) were created using FSL and the following procedure: registering the tissue template in MNI space to native space using FSL prior tissue probability maps, finding overlap between the tissue probability maps and the tissue template created in the previous step, applying a 0.4 threshold and binarizing the tissue templates, and finally generating the tissue masks by applying the prior in native space to the binarized tissue probability map.

The EPI images were deobliqued and reoriented into RPI using AFNI, and skull stripped with FSL BET. Slice time correction was performed with AFNI's 3dTshift. AFNI's 3dTstat was used to obtain mean intensity values over all timepoints for each voxel (base image). Two pass motion correction was performed on the data using AFNI's 3dvolreg. For each volume the image was aligned with the base mean image, providing motion displacement and movement parameters. Voxel wise statistics for the motion corrected output from this step were used as the base for the second pass motion correction using 3dvolreg and a Fourier transformation to obtain the motion and displacement parameters. The images were registered to the subject's T1 scan using FLIRT, and subsequently normalised to MNI space. The normalized images were smoothed with AFNI's 3dmerge using a 6mm FWHM kernel. Nuisance regression to remove noise signals from the data was performed using AFNI's 3dDeconvolve and 3dTproject. For this step, the motion parameters were demeaned, and motion parameter derivatives were calculated. The CSF and WM masks were resampled into functional space using AFNI's 3dresample and respective time courses were extracted. The

demeaned 6 motion parameters, the 6 motion derivatives and the CSF and WM signal were regressed out of the data with AFNI. Subjects with motion exceeding 3mm were removed from the neuroimaging sample, resulting in a total sample of 22 participants in the HS group and 22 participants in the LS group (the behavioural data from these subjects was still used in the computational analyses).

5.2.12. fMRI analysis

Single-subject fMRI analyses were conducted using the general linear model (GLM) as implemented in FSL FEAT (Woolrich, Ripley, Brady, & Smith, 2001). Base regressors for the task were defined in terms of the onsets of the decision period, which had a variable duration (the response time) and the outcome period, which had a fixed duration (2s). The decision period regressor was accompanied by four parametric modulator regressors encoding for the subject's trial-wise prediction of outcome, uncertainty at the 1st level of the HGF, expected volatility at the 3rd level and the predicted environmental uncertainty about the advice. The outcome period regressor was associated with three parametric modulators encoding for the absolute outcome-related precision-weighted PE ($\varepsilon_2^{(t)}$; see Iglesias et al., 2013), uncertainty at the 2nd level ($\sigma 2$) and the volatility-related precision-weighted PE ($\varepsilon_3^{(t)}$). All parametric modulators were Z-normalised (zero mean, unit standard deviation) and demeaned before entering into the GLM. Temporal and dispersion derivatives of all regressors were added to the GLM of each subject in order to account for variability in the onset and width of hemodynamic responses. We also included the six rigid-body realignment parameters representing head motion as regressors of no interest in the GLM for each subject.

Group analyses were conducted using second level GLMs as implemented in FSL FEAT (Woolrich, Behrens, Beckmann, Jenkinson, & Smith, 2004). Decision-related contrast estimates (expected volatility at the 3rd level, predicted environmental uncertainty about the

advice) and outcome-related contrast estimates (ε_2^((t)); ε_3^((t))) from the subject-level analysis were of interest at the group level. Contrasts of interest at the group level examined, for each computational regressor, (i) the average activation across groups (HS + LS) and (ii) significant differences between groups (HS vs LS, adjusted for CP covariate). As informed by previous results of ε2 and ε3 investigations (Iglesias et al., 2013; Diaconescu et al., 2017; Mathys et al, 2014) we further restricted the group contrasts of these parameters to a priori region of interest using a masque of the dopaminergic midbrain. For each contrast, we corrected for multiple comparisons using family-wise error (FWE) correction at the cluster-level ($p < 0.05$).

5.3. Results

5.3.1. Descriptive and behavioural analysis

Table 3 provides a summary of the demographic and questionnaire data. Mixed ANOVA models were used to investigate behavioural performance in the task. There was a main effect of phase ($F(1,51) = 19.28$, $p < 0.01$, *eta squared* = .15), a main effect of cue type ($F(1,51) = 35.59$, $p < 0.01$, *eta squared* = 0.2) and a significant interaction between them ($F(1,51) = 17.08$, $p < 0.01$, *eta squared* = 0.3) on accuracy in the task. Accuracy was significantly higher in stable conditions (M = 0.54, SD = 0.01) and in response to advice cue (M = 0.52, SD = 0.01). Similar results were obtained for advice taking (% going with the advice cue). There was a main effect of phase ($F(1,51) = 11.51$, $p < 0.01$, *eta squared* = .05) and main effect of cue type ($F(1,51) = 9.61$, $p < 0.03$, *eta squared* = 0.01). Advice taking was significantly higher during stable phases (M = 0.64, S = 0.02) and in accordance to the advice cue phases (M = 0.62, SD = 0.02). There were no group differences for these behavioural parameters.

Table 3. Demographic and questionnaire data across the HS and LS groups.

Characteristic	LS (n = 26)	HS (n=27)	t/χ2	p
Gender(male/female)	7/19	10/17	0.55	0.40
Age (years)	20.63 (SD = 2.20)	19.51(SD= 1.25)	1.10	0.31
IQ score	93.78(SD = 9.20	95.12 (SD = 9.26)	0.63	0.52
SDS	5.96 (SD = 1.52)	4.86 (SD = 2.33)	1.86	0.07
SPQ Total	7.61 (SD = 3.60)	46.64 (SD = 5.23)	-29.25	< 0.01
SPQ Cognitive Perceptual Factor	2.83 (SD= 2.01)	20.41 (SD = 5.22)	-15.02	< 0.01
SPQ Interpersonal Factor	3.57 (SD = 2.48)	20.86 (SD = 4.44)	-16.22	< 0.01
SPQ Disorganised Factor	1.91 (SD = 2.42)	10.77 (SD = 2.82)	-11.29	< 0.01

The behavioural results match the reports from the debriefing. Participants overwhelmingly reported that they believed they were playing another person (94% of participants answered “yes”). A total of 96% of the participants indicated that they primarily relied on the advice when making their outcome predictions.

5.3.2. Behavioural Modelling

Bayesian model selection gave a clear result, showing that the mean-reverting HGF with a response model incorporating volatility mapping (M8) was more likely to explain task behaviour than any other model (Fig. 2B). Importantly, model selection results were equivalent in both groups, allowing for a direct comparison of parameter estimates across groups. We thus carried out group comparisons for the recoverable parameters, namely all perceptual

parameters related to advice and all the response model parameters. We carried out ANCOVAs (CP scores included as covariates) to assess group differences.

The response parameters were similar between the two groups. However, we identified significant differences between HS and LS participants for $\mu_3^{(t=0)}$ ($F(1,50) = 5.55$, $p < 0.02$, *eta squared* = 0.1) , ϑ ($F(1.50) = 4.41$, $p < 0.04$, *eta squared* = 0.08) and ω as related to the advice ($F(1,50) = 6.2$, $p < 0.01$, *eta squared* = 0.1). The HS group compared to the LS group presented with significantly higher $\mu_3^{(t=0)}$ (M = 1.06, SD = 0.08, 95% CI = 0.96-1.15) and significantly higher ω (M = -3.42, SD = 1.21, 95% CI = -5.85- -0.99) for advice compared to the LS, but with lower ϑ (M = 0.61, SD = 0.01, 95%CI = 0..60-0.62, Fig 4).

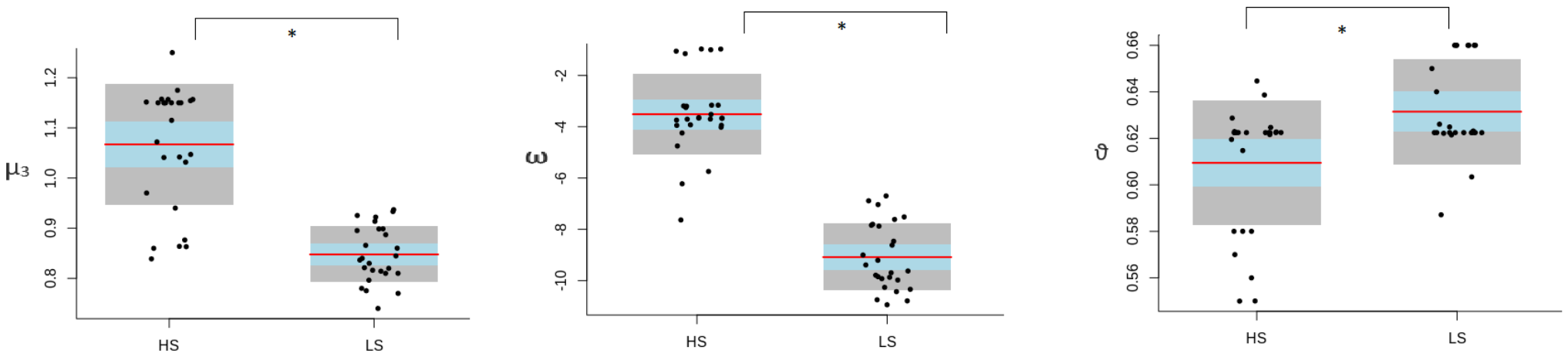

Fig 4. Group differences for the means of the $\mu_3^{(t=0)}$, ω and ϑ for the advice learning model. There are higher estimates of μ_3 and ω for advice in the HS group compared to the LS group, and lower ϑ estimates in the HS compared to the LS group. All group differences were significant at a 0.05 Bonferroni correction level (*). Jittered raw data are plotted for each parameter. The solid red line refers to the mean, the light blue background reflects the 95% confidence intervals of the mean, the grey bars reflect 1SD of the mean.

We further investigated group × task phase interaction effects on the phase-specific averages (for the advice learning model, CP entered as a covariate) of the prediction about advice accuracy ($\hat{\mu}_1^{(t)}$), the predicted adviser ($\mu_3^{(t-1)}$), the absolute advice precision-weighted PE ($\varepsilon_2^{(t)}$) and the signed volatility precision-weighted PE ($\varepsilon_3^{(t)}$).

There was a significant group × phase interaction (F(1,50) = 5.56, P < 0.02, *eta squared* = 0.9) and significant main effect of phase (F(1,50) = 99.9, p < 0.01, *eta squared* = 0.63) for the predicted advice accuracy or $\hat{\mu}_1^{(t)}$. This suggested that the HS group showed a larger impact of phase on predictions about advice accuracy compared to the LS group (Fig 5). Additionally, there was a significant group × phase interaction (F (1,50) = 5.86, p < 0.02, *eta squared* = 0.4) and a significant main effect of phase (F (1,50) = 13.43, p < 0.01, *eta squared* = 0.09) for the predicted adviser volatility $\mu_3^{(t-1)}$. The HS group showed larger $\mu_3^{(t-1)}$ estimates for the volatile condition (M = 1.45, SD = 0.11, 95% CI = 1.23-1.67, p < 0.01) compared to any other group × phase design cell (Fig 5). These results are in line with the group parameter effects, which suggest that HS tend to perceive the adviser's intentions as more volatile and update those beliefs to a lesser degree than LS. At the same time, due to the hierarchical nature of the model, enhanced volatility estimates (and enhanced evolution rate at the second level, about the adviser fidelity) promote larger learning rates in HS compared to LS. Thus, HS also update their beliefs about the advice more accuracy more quickly, showing larger effects of volatility on the estimated advice accuracy.

There were no significant effects detected for $\varepsilon_2^{(t)}$, but there was a significant group × phase interaction (F (1,50) = 5.71, p < 0.02, *eta squared* = 0.05) and a significant main effect of group (F (1,50) = 7.22, p < 0.01, *eta squared* = 0.07) for $\varepsilon_3^{(t)}$. Post-hoc analysis revealed that, similarly to the analysis of $\mu_3^{(t-1)}$, that the HS group presented with the highest $\varepsilon_3^{(t)}$during

volatile phases (M = 1.03, SD = 0.24, 95% CI = 0.54-1.52, p < 0.02) compared to all other design cells. The HS also presented with higher $\varepsilon_3^{(t)}$ during the stable conditions of the task (M = 0.48, SD = 0., 95% CI = -0.01-0.97, p < 0.03) compared to both LS volatile and LS stable estimates (Fig 5).

Finally, we also investigated whether participants from both groups weighed the advice more than the reward cue by testing whether the model parameter ζ, i.e. the additional bias toward the social cue, was significantly different from log(1). Zeta values (M = 0.67, SD = 1.04) were significantly different from 0, t (52) = 4.68, p < 0.001, Cohen's d = 0.64. Zeta values higher than log(1) suggest that participants relied predominantly on the advice rather than the social cue. The card cue affected learning in the different phases of the task, but there were no significant group differences on any parameters when learning from the card cue (i.e. subjects learned similarly about the reward cue probabilities).

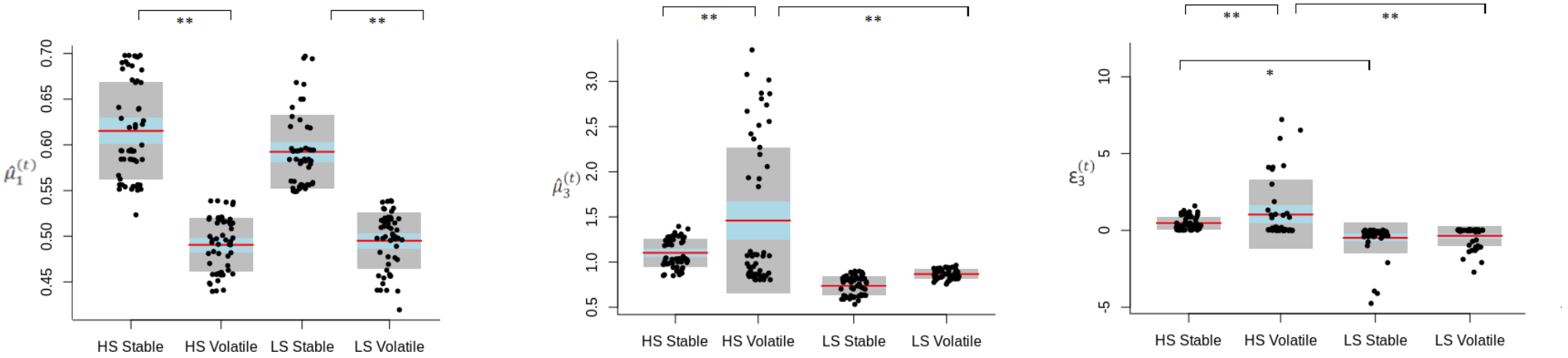

Fig 5. Significant group x phase interactions for the $\hat{\mu}_1^{(t)}$, $\hat{\mu}_3^{(t)}$ and $\varepsilon_3^{(t)}$. There was a significant main effect of phase and a significant group x phase interaction for all three analyses. The HS group had significantly higher $\hat{\mu}_1^{(t)}$ for the stable conditions of the task compared all other design cells including HS volatile. The HS group showed a significantly higher value in the volatile condition (for both $\hat{\mu}_3^{(t)}$ and $\varepsilon_3^{(t)}$) compared to any other design cell. The HS group also showed significantly higher ε_3 levels for stable conditions, compared to both LS stable and LS volatile. Jittered raw data are plotted for each parameter. The solid red line refers to the mean, the light blue background reflects the 95% confidence intervals of the mean, the grey bars reflect 1SD of the mean. Significance is presented at < 0.05 (*) and < 0.01 (**).

5.3.3. fMRI, activations across the sample

When pooling the results across the whole sample, we found that the computational regressor associated with the expected adviser volatility at the 3rd level ($\mu_3^{(t-1)}$) activated a wide range of regions including the precentral gyrus, a part of the cerebellum, middle and superior temporal gyri, anterior cingulate and parahippocampal gyri, inferior frontal gyrus, thalamus and cuneus ($p < 0.05$, whole-brain cluster-level FWE corrected, Table 4, Fig 6A). The expected uncertainty associated with advice ($w_2^{(t)}$) activated parts of the posterior cingulate cortex and the cuneus (Table 4, Fig 6B).

Across the sample, effects of low-level (advice) precision-weighted PEs ($\varepsilon_2^{(t)}$) were found in the insula, striatum (putamen), thalamus, cerebellum, superior and middle frontal gyri, middle temporal gyrus, anterior and posterior cingulate cortexes and the midbrain ($p < 0.05$, whole-brain cluster-level FWE corrected, Table 4, Fig 7A). Effects associated with the volatility-related precision-weighted PEs ($\varepsilon_3^{(t)}$) were observed in the brainstem, anterior cingulate cortex, superior frontal gyrus and cerebellum ($p < 0.05$, whole-brain cluster-level FWE corrected, Table 4, Fig 7C).

Table 4. Regions showing main effects of activations for the computational regressors of interest.

Computational regressor fMRI activations	Brain Region	Cluster Size	p (FWE-corrected)	Z-value of peak voxel	x,y,z coordinates (MNI)
$\mu_3^{(t-1)}$	R Precentral Gyrus	3250	< 0.001	5.58	2, -40, 66
	Cerebellum	2275	< 0.001	5.16	-6, -84, -34
	L Middle Temporal Gyrus	2046	< 0.001	5.01	-52, -62, 6
	R Precentral gyrus	763	< 0.001	3.97	50, -10, 48
	Anterior Cingulate Gyrus	422	< 0.001	4.14	-2, 36, 12

	R Inferior Lateral Occipital Cortex	334	< 0.001	4.1	46, -74, 4
	R Superior Temporal Gyrus	273	< 0.001	4.23	60, -24, 8
	R Inferior Frontal Gyrus	227	< 0.001	4.13; 3.98	58, 24, 18; 58, 16, 16
	R Thalamus	138	0.003	4.3; 3.83	6, -22, 0; 8, -10, 4
	R Cuneus	122	0.006	4.28	14, -84, 20
	L Parahippocampal Gyrus	97	0.02	3.84; 3.58	-30, -24, -24; -26, -28, -24
$w_2^{(t)}$	R Posterior Cingulate Cortex	339	< 0.001	4	6, -68, 16
	L Cuneus	152	< 0.01	3.86	-2, -84, 34
$\varepsilon_2^{(t)}$	L Insula	11420	< 0.01	4.06	-44, 12, -6
	R Putamen		< 0.01	5.56	24, -4, 12
	L Cerebellum	286	<0.001	3.61	-4, -68, -12
	R Cerebellum	169	<0.001	4.23	22, -82, -22
	L Superior Frontal Gyrus	205	< 0.001	3.95	-16, -12, 62
	L Superior Parietal Lobule			3.76	-22, -40, 58
	R Middle Temporal Gyrus	199	< 0.01	5.05	50, -38, -4
	L Middle Frontal Gyrus	2871	< 0.01	4.18	-44, 30, 36
	L Thalamus		< 0.01	4.47	-14, -26, -6
	L Midbrain	2316	< 0.01	3.97	-8, -24, -12
	Anterior Cingulate Gyrus	998	< 0.01	3.91	4, 28, 24
	Posterior Cingulate Gyrus	79	< 0.01	3.5	-2, -32, 30
$\varepsilon_3^{(t)}$	L Cerebellum		< 0.01	1.56	-10, -44, -40
	R Brainstem	2885	< 0.01	5.59	10, -32, -26
	R Superior Frontal Gyrus	2061	< 0.01	4.27	24, -6, 56
	L Anterior Cingulate Gyrus	1125	< 0.01	4.32	4, 32, 0
	L Posterior Cingulate Gyrus	68	< 0.01	1.44	-2, -32, 28

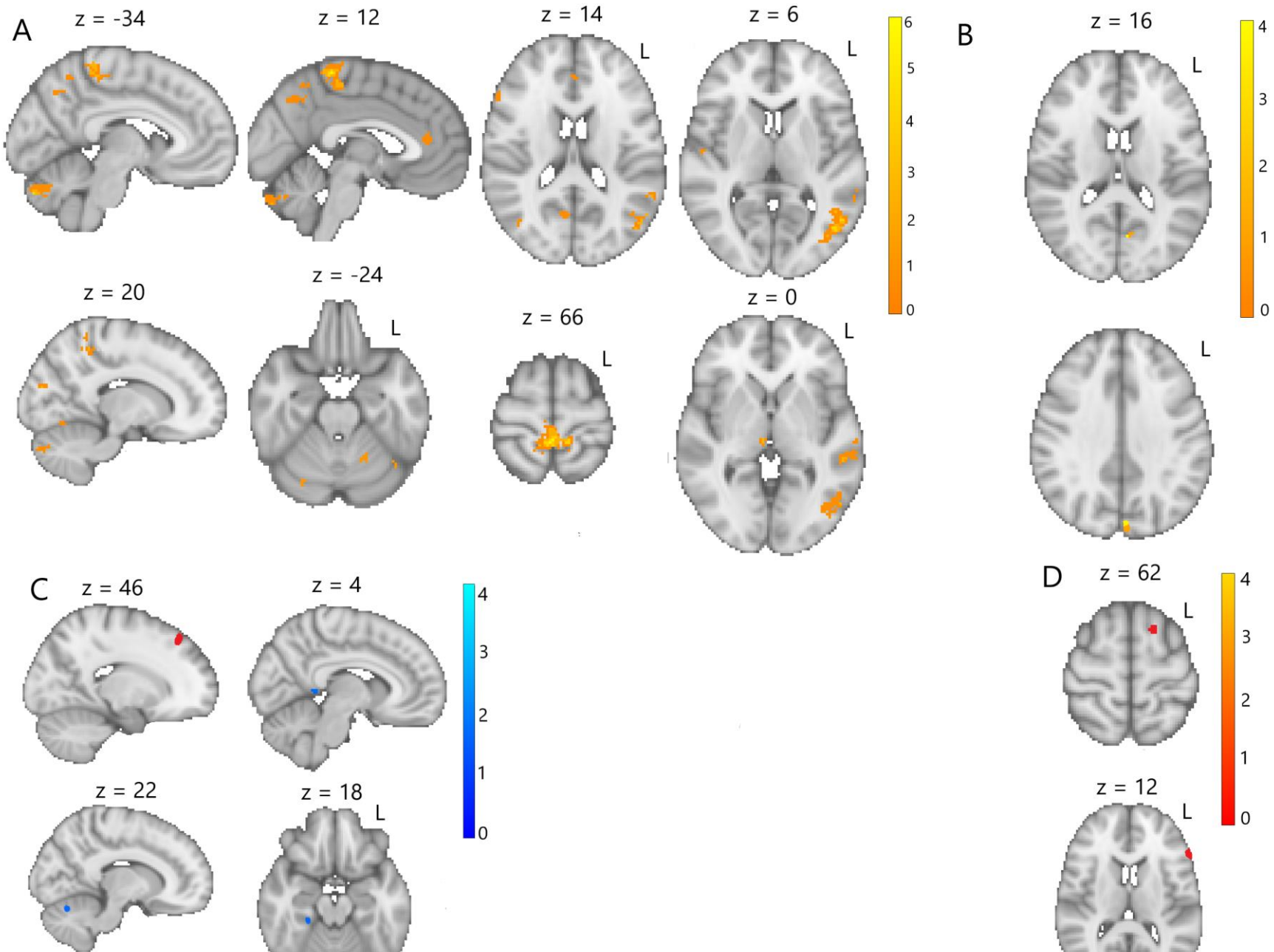
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Fig 6. **Cue-related Activations**: The neural representation of expected adviser volatility, $\mu_3^{(t-1)}$, and environmental uncertainty about the advice, $w_2^{(t)}$. All activation maps are overlaid on anatomical MNI standard brain and represent activations surviving cluster-level FWE-corrected activations at $p < 0.05$. Colour bars represent z-statistics. (A) A representative map of significant decision-related activations modulated parametrically by $\mu_3^{(t-1)}$, calculated via one-sample t-test (n = 44) at a group-level. (B) A map of significant group-level decision-related activations modulated by $w_2^{(t)}$. (C) Significantly greater representation of $\mu_3^{(t-1)}$-related activation in regions as assessed by independent samples t-tests (22 HS and 22 LS), red colour indicates activity higher in HS compared to LS, blue represents activity higher in LS compared to HS. (D) Significantly greater representation of w-related activation in regions during group comparisons, red represents activity higher in HS compared to LS.

5.3.4. fMRI data, group differences adjusted for CP

Under whole-brain FWE-correction for multiple comparisons, a number of whole-brain group differences were detected for the computational regressors of interest. All differences are significant at a $p < 0.05$ whole-brain cluster-level FWE correction (cluster extend threshold $z > 1.0$) . The right superior frontal gyrus showed a higher activation in the HS compared to the LS subjects in response to expected adviser volatility ($\mu_3^{(t-1)}$) (Table 5). In comparison, LS subjects showed a higher activity for this parameter in the posterior cingulate gyrus, the cerebellum and the parahippocampal gyrus (Table 5, Fig 6C). In response to the predicted environmental uncertainty about the advice $w_2^{(t)}$, the HS subjects presented with higher activity in the superior/inferior frontal gyrus and the inferior temporal gyrus (Table 5, Fig 6D).

The HS subjects presented with increased activity in the middle frontal gyrus and the anterior cingulate gyrus in association with low-level precision-weighted PEs ($\varepsilon_2^{(t)}$, Table 5, Fig 7B). In contrast, LS subjects showed higher activity, compared to HS subjects, in the superior and middle temporal gyri, insula and thalamus (Table 5, Fig 7B).

Similarly, HS subjects presented with higher middle frontal gyrus activity in response to high-level volatility precision-weighted PEs ($\varepsilon_3^{(t)}$, Table 5, 7D). LS subjects showed higher activity in the paracingulate gyrus, insula, middle and superior temporal gyri (Table 5, Fig 7D). An additional region of interest analysis, using anatomically defined *a priori* masks of the dopaminergic and cholinergic brainstem (Bunzeck and Düzel, 2006; Iglesias et al., 2013) revealed significantly higher activations in LS subjects, compared to HS subjects in these regions of the brainstem, for both $\varepsilon_2^{(t)}$and $\varepsilon_3^{(t)}$, respectively (small volume FWE-corrected $p < 0.05$, Fig 7D).

Table 5. Regions showing group differences in activations across computational regressors of interest.

Computational regressor fMRI activations	Contrast	Brain Region	Cluster Size	p (FWE-corrected)	Z-value of peak voxel	x,y,z coordinates (MNI)
$\mu_3^{(t-1)}$	HS > LS	R Superior Frontal Gyrus	5650	< 0.001	3.56	18, 34, 46
	LS > HS	R Posterior Cingulate Gyrus	1851	< 0.01	3.18	8, -44, 4
		R Cerebellum		< 0.01	2.99	12, -66, -22
		R Parahippocampal Gyrus			2.98	24, -34, -18
$w_2^{(t)}$	HS > LS	L Superior Frontal Gyrus	35960	< 0.001	3.86	-18, 12, 62
		L Inferior Temporal Gyrus			3.69	-64, -38, -22
		L Inferior Frontal Gyrus			3.66	-58, 24, 12
$\varepsilon_2^{(t)}$	HS > LS	L Middle Frontal Gyrus	121	< 0.01	2.1	-34, 28, 38
		L Anterior Cingulate Gyrus	45	< 0.01	1.49	-4, 22, 22
	LS > HS	L Midbrain	30	< 0.01	1.35	-4, -15, -8
		Superior Temporal Gyrus	94	< 0.01	2.11	55, -24, -4
		R Superior Temporal Gyrus	71	< 0.01	1.77	56, 4, -12
		L Insula	69	< 0.01	2.06	-44, 12, -4
		L Thalamus	30	< 0.01	1.51	-2, -14, -4
		R Middle Temporal Gyrus	30	< 0.01	2.51	46, -58, 12
		R Insula	32	< 0.01	1.52	40, 12, -12
$\varepsilon_3^{(t)}$	HS > LS	L Middle Frontal Gyrus	675	< 0.01	2.43	-48, 8, 42
	LS > HS	Paracingulate Gyrus	517	< 0.01	3.09	0, 38, 22
		L Insula	209	< 0.01	2.91	-40, 0, -14
		R Brainstem	21	< 0.01	1.59	8, -26, -22
		R Middle Temporal Gyrus	155	< 0.01	2.18	50, -52, 14
		L Superior Temporal Gyrus	69	< 0.01	2.31	-54, -28, 2
		R Superior Temporal Gyrus	49	< 0.01	1.91	56, -26, -2

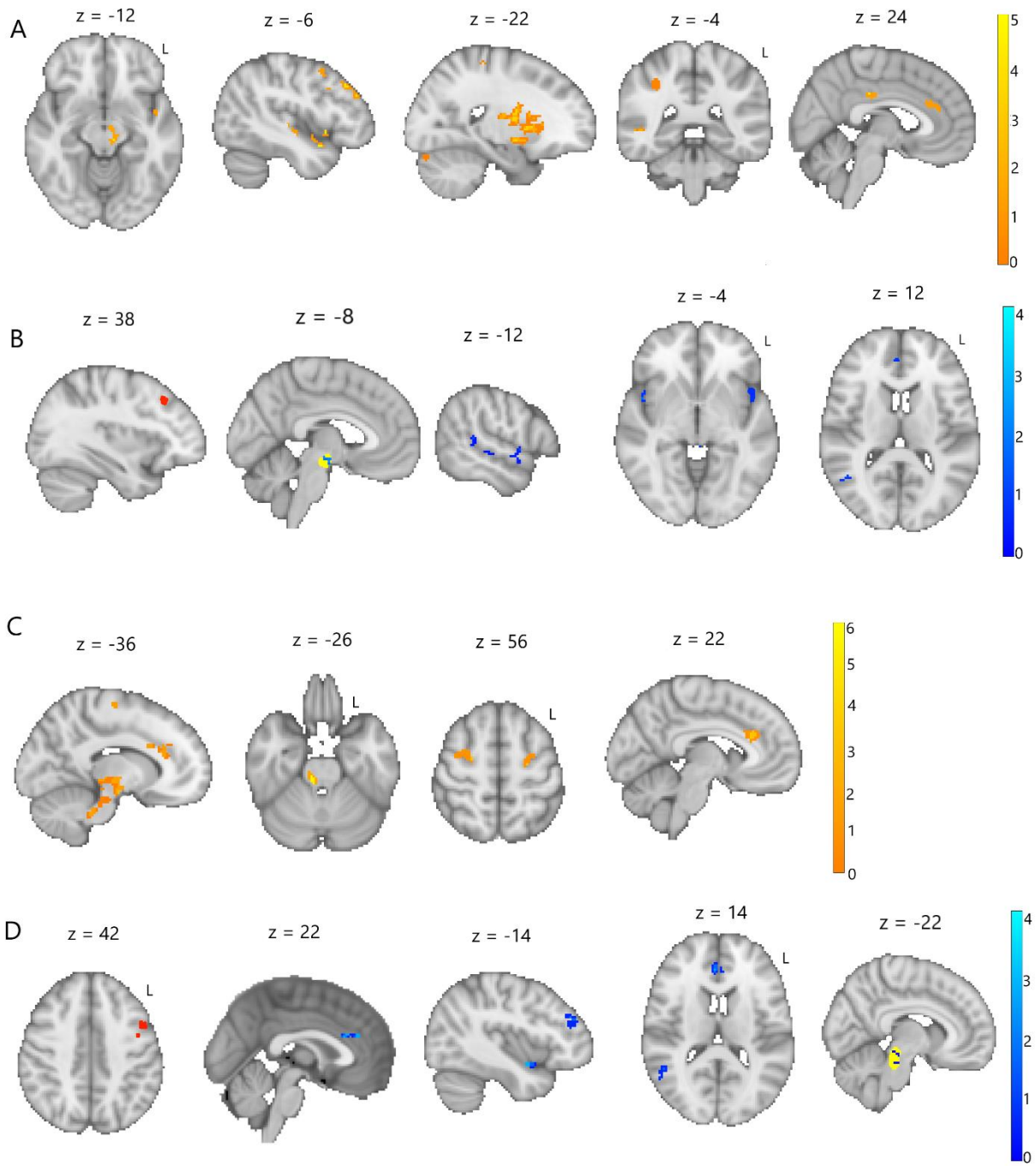


Fig 7. **Outcome-related Activations**: The neural representation of low-level precision weighted prediction errors, $\varepsilon_2^{(t)}$, and high-level precision-weighted prediction errors, $\varepsilon_3^{(t)}$. All activation maps are overlaid on anatomical MNI standard brain and represent activations surviving cluster-level FWE-corrected activations at $p < 0.05$. Colour bars represent z-statistics. (A) A representative map of significant outcome-related activations modulated parametrically by $\varepsilon_2^{(t)}$, calculated via one-sample t-test (n = 44). (B) Significantly greater representation of $\varepsilon_2^{(t)}$-related activation in regions as assessed by independent samples t-tests (22 HS and 22 LS), red colour indicates activity higher in HS compared to LS, blue represents activity higher in LS compared to HS. Yellow underlay represents the a-priori midbrain mask used. (C) A representative map of significant outcome-related activations modulated parametrically by $\varepsilon_3^{(t)}$, calculated via one-sample t-test (n = 44). (D) Significantly greater representation of $\varepsilon_3^{(t)}$-related activation in regions as assessed by independent samples t-tests (22 HS and 22 LS), red colour indicates activity higher in HS compared to LS, blue represents activity higher in LS compared to HS. Yellow underlay represents the a-priori midbrain mask used.

5.4. Discussion

We aimed to investigate social learning under volatility in HS individuals using computational modelling and fMRI analyses. The winning model was identical across HS and LS individuals and indicated that task behaviour was driven by predictions about the advice rather than the individual sampling of card outcomes, as indicated by the zeta parameters being significantly larger than zero. HS subjects were characterised by significantly higher initial priors for volatility ($\mu_3^{(t=0)}$) as well as lower learning rate regarding meta-volatility. Firstly, computational modelling of behaviour between groups indicated that, HS subjects show abnormal learning from volatility. Secondly, fMRI results, indicate aberrantly attenuated encoding of both low-level and high-level precision-weighted PEs in HS individuals. Our results are in line with previous work suggesting that psychosis may be associated with aberrant learning about volatility impacting belief formation (Cole et al., 2020; Corlett et al., 2010; Powers et al., 2017; Reed et al., 2020; Sterzer et al., 2018).

As in previous fMRI work in schizotypy, we found no behavioural group differences in behavioural performance (Kozhuharova et al., 2020). Computational modelling of participants' behaviour revealed that HS individuals were characterized by higher initial priors for volatility ($\mu_3^{(t=0)}$) suggesting that they expected the advice to be volatile than LS individuals. Furthermore, they tended to stick to those beliefs more than LS individuals, as they displayed reduced meta-volatility or ϑ parameter estimates suggesting reduced belief updating about volatility. These parameter group results are consistent with the group × phase interactions on the estimated volatility of the adviser. HS individuals showed larger estimates of volatility, which were particularly pronounced as they transitioned from stable to volatile task phases. These effects on volatility estimates suggest that HS individuals tend to rely more

on their higher-level prior expectations than on sensory inputs, when predicting the adviser volatility.

In turn, this increased sense of volatility was related to heightened belief updating about the adviser fidelity. In contrast to LS, HS individuals showed an increased evolution rate about fidelity or ω parameter estimates. These parameter differences were consistent with the increased effects of task phase on adviser accuracy predictions, suggesting that HS individuals in contrast to LS individuals change their beliefs more quickly as a function of outcome-related PEs.

Finally, we found no group differences for the social bias parameter ζ, suggesting that both groups put equal weight on the learned social prediction relative to the learned reward probability estimation when making decisions. Thus, our results suggest that biases in social functioning in schizotypy (Ettinger et al., 2014; Miller & Lenzenweger, 2012) are not simply an abnormality in how much social cues are weighted but arise from abnormal hierarchical learning about social cues.

In line with previous work in hierarchical learning under volatility in CHR individuals (Cole et al., 2020) and schizophrenia patients (Adams et al., 2013; Powers et al., 2017; Woodward, Moritz, Cuttler, & Whitman, 2006), our findings in high schizotypy subjects suggest that the this risk cohort for psychosis show an increased estimation of volatility (according to the behavioural data) during social learning. Heightened prior predictions of volatility lead to a heightened uncertainty about advice-outcome associations, leading to increased learning rates about outcomes and an increased adoption of lower-level precision-weighted PEs.

This heightened belief about the volatility of social information necessitates hypervigilance and potentially makes it difficult to update social associations. If HS individuals

rely mainly on higher level volatility priors of social information and adhere to expectations over evidence, this could be a potential mechanism, explaining the social difficulties observed in these populations (Miller & Lenzenweger, 2012). Recent work has reported that, similarly to schizophrenia patients, high schizotypy individuals have impairments in friendship relations, family relations and interpersonal engagement even when cognitive and emotional skills are unaffected (Aghvinian & Sergi, 2018). Our results would suggest that the learning mechanisms that would drive these relationships are impaired in HS individuals, leading to abnormal hypervigilance as driven by the expectation of over-volatility. Similarly, these results could explain the aberrant salience deficits and jumping to conclusion biases observed in schizotypy samples (Chun, Gross, Mielock, & Kwapil, 2020; Chun, Kwapil, & Brugger, 2019; Cicero, Becker, Martin, Docherty, & Kerns, 2013; Haselgrove et al., 2016; Juarez-Ramos et al., 2014; O'Tuathaigh et al., 2020; Sellen, Oaksford, & Gray, 2005). Similar computational models have been used to explain aberrant salience in schizophrenia patients as well, where higher-order beliefs of abnormally low precision render the environment seemingly unpredictable (e.g. more volatile; Adams et al., 2013).

The neural pattern of activation in response to these computational parameters further suggests an altered representation of volatility, thus supporting the notion of aberrant hierarchical learning in HS samples. As in previous work, we found that volatility estimates ($\mu_3^{(t-1)}$) activated a network of regions across the cerebellum, cuneus, temporal gyri and parahippocampal gyri (Cole et al., 2020; Powers et al., 2017). Group contrasts at this level showed that activations in these areas are higher in LS subjects compared to HS subjects. On the other hand, HS subjects showed higher representation of volatility estimates in the superior frontal gyrus. While the behavioural results indicate that HS subjects present with higher estimated volatility during volatile task phases, they also presented with lower meta-volatility

across the whole task – i.e., reduced learning about volatility. Thus, these relative deactivations in key neural regions in HS participants during decision-making suggests an atypical cortical representation of environmental volatility in schizotypy.

Our investigations of lower-level precision-weighted PEs across the sample shows effects consistent with previous studies, with key activated regions including midbrain, cerebellum, middle frontal gyrus, middle temporal gyrus, anterior cingulate cortex and insula (and activations in the cholinergic brainstem in response to higher-level prediction errors; Cole et al., 2020; Iglesias, et al., 2013, Diaconescu et al., 2017). Crucially, group contrasts show that HS subjects present with attenuated neural processing of both low-level and high-level precision-weighted PEs. LS subjects showed higher activity in the midbrain, insula, middle and superior temporal gyri in response to low-level precision-weighted PEs, while HS subjects showed higher activity in the anterior cingulate cortex and the middle frontal gyrus. Similar results were observed for high-level PEs, where LS subjects presented with higher activity in the cholinergic brainstem, insula, paracingulate gyrus and middle/superior temporal gyrus and HS subjects presented with higher activity in the middle frontal gyrus. One possible explanation for the observed underweighting (in terms of neural encoding) of low-level PEs could be that HS subjects overweight low-level PEs and underweight high-level PEs. One mechanistic explanation for the observed underweighting (in terms of neural encoding) of low-level precision-weighted PEs could be that HS may be characterised by abnormal estimates of environmental uncertainty as observed for the behavioural data, i.e. they overweight low-level PEs. HS subjects also presented with underweighting of high-level PEs relative to LS subjects, suggesting that they inform updates of volatility estimates in an aberrant way.

Group comparisons across all computational parameters of interest showed an increased activity in frontal regions in HS subjects compared to LS subjects, including the

middle, inferior and superior frontal gyri, as well as parts of the anterior cingulate cortex. Activations of the prefrontal cortex have been reported when participants simulated others' intentions (Behrens et al., 2008; Frith and Frith, 2006, 2012) and decisions (Nicolle et al., 2012) and are commonly associated with a broad network responsive for mentalizing and Theory of Mind cognition (Ochsner, 2008; Phan et al., 2002). The current findings of increased frontal activity for estimated volatility and low- and high-level precision-weighted PEs in HS subjects are in line with the majority of previous work in social cognition in schizotypy samples showing abnormal response of the mPFC to social cues (see Kozhuharova et al., 2020 for a review). The consistent patterns of increased activity in PFC regions in HS samples during a social cognition task further supports the notion that the HS state is characterised by abnormal processing of socially salient cues leading to aberrant beliefs about others and thus contributing to the formation of delusions (Morrison et al., 2004, Corlett et al., 2010). In line with these findings, we also observed a higher representation of environmental uncertainty in superior frontal regions. HS subjects presented with increased activity in the superior/inferior frontal gyri, indicating that they process (uncertainty) of social information abnormally.

Previous work has shown that the high end of the schizotypy continuum is at an increased risk for developing psychosis (Raine 1991; Salokangas et al., 2013). Thus, the comparison of high vs. low schizotypy implemented here may inform investigations of abnormalities that are of particular importance for the schizophrenia continuum. Furthermore, the neural and behavioral results reported here used CP (positive schizotypy subfactor scores) as a covariate. Thus, in comparison to previous work focusing mainly on the positive symptoms of schizotypy (Debbané, van der Linder, Gex-Fabry, & Eliez, 2009; Kerns, 2005; Modinos et al., 2017; Waltmann et al., 2019) here we show that a combination of schizotypy subfactors matches the findings of abnormal hierarchical (behavioral and neural) learning and abnormal processing of uncertainty observed in clinical samples (Adams et al., 2013; Corlett et al., 2007;

Corlett et al., 2009; Corlett et al., 2010; Ermakova et al., 2018; Gradin et al., 2011; Murray et al., 2008; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006; Schultz, Dayan, & Montague, 1997; Cole et al., 2020). As such, investigations of high schizotypy samples (which are potentially easier to recruit than CHR and FEP samples) may inform risk for psychosis and protective factors.

Similar to previous uses of these paradigms (Diaconescu et al., 2014, Sevgi et al, 2020), our experimental design can be limited to level 1 of theory of mind inference (inferring the mental state of advisor) as advice was provided in the form of a social cue on screen removing the recursive nature of social inference (i.e. higher level "I think what he thinks what I think" theory of mind). This may not necessarily be a disadvantage as it restricts the conclusions drawn from this study to a particular level of social inference and it meets the aims of the work (i.e. investigating whether hierarchical learning – in particular predictions about volatility - are affected in HS subjects similarly as in clinical samples) and allows for straightforward application of efficient models like the HGF. Yet, this approach limited the conclusions drawn from this study to a particular level of social cognition.

In summary, the current work shows that HS subjects present with abnormal social learning under uncertainty, specifically increased volatility estimates and attenuated neural encoding of both low-level and high-level PEs. HS subjects expected the environment (i.e. social advice) to be more volatile and they tended to rely more on prior beliefs about volatility than actual task feedback. By relying more on their expectations of volatile advice, HS subjects updated too quickly about the advice accuracy, but slower belief updates about higher-level advice volatility. Thus, they initially perceived advice to be volatile and tended to rely on those prior beliefs. This was supported by abnormally attenuated processing of higher-level volatility PEs, which drive updates about volatility. Taken together, the results strongly suggest that HS

subjects present with atypical cortical representation of volatility and abnormal learning from uncertainty.

Chapter Six

High schizotypy traits are associated with reduced hippocampal resting state functional connectivity.

Abstract

Altered hippocampal functioning is proposed to play a critical role in the development of schizophrenia-spectrum disorders. Previous resting state functional Magnetic Resonance Imaging (rs-fMRI) studies report disrupted hippocampal connectivity in patients with psychosis and in individuals with clinical high risk, yet hippocampal connectivity has not been investigated in people with high schizotypy traits. Here we used rs-fMRI to examine hippocampal connectivity in healthy people with low (LS, n = 23) and high levels (HS, n = 22) of schizotypal traits assessed using the Schizotypy Personality Questionnaire. Using a bilateral hippocampal seed region, we examined resting state functional connectivity (RSFC) between hippocampus and striatal, thalamic and prefrontal cortex regions of interest. Compared to LS, HS participants showed lower RSFC between hippocampus and striatum and between hippocampus and thalamus.

Whilst the group effect of reduced hippocampal RSFC in striatal and thalamic regions was driven by total schizotypy scores, positive schizotypy subfactor scores were significantly positively correlated with hippocampus-caudate/thalamus RSFC. Group differences in RSFC were not observed between hippocampus and prefrontal cortex. These results demonstrate that subclinical schizotypal traits are associated with altered hippocampal connectivity in striatal and thalamic regions and provide further support that hippocampal dysconnectivity confers risk for schizophrenia spectrum disorders.

6.1. Introduction

There is a growing consensus that psychosis exists on a continuum ranging from subclinical psychotic-like experiences in the general population to full-blown symptoms in clinical samples (Linscott & Van Os, 2013; Nelson, Seal, Pantelis, & Phillips, 2013; Yung et al., 2009). Subclinical psychotic-like experiences in healthy people, commonly referred to as schizotypy, represent a latent personality organization reflecting an underlying vulnerability to developing schizophrenia-spectrum disorders (Kwapil, Gross, Silvia, & Barrantes-Vidal, 2013; Miller et al., 2002; Debbané et al., 2015; Chapman, Chapman, Kwapil, Eckblad, & Zinser, 1994). Furthermore, people with high schizotypy (HS) have an elevated risk of developing psychosis compared to the general population, with studies estimating that around 2% of these individuals meet criteria for a schizophrenia-spectrum diagnosis at a 10-year follow-up, approximately double the risk in the general population (Kwapil et al., 2013; Van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009). Thus, investigating schizotypal traits in non-clinical samples may provide important information about aetiological mechanisms underlying risk for psychosis, without the presence of clinically common confounders (i.e. medication, comorbidity). A better understanding of neurobiological mechanisms may provide useful knowledge that helps us to develop early detection strategies, biomarkers and preventive interventions for those at risk of psychosis (Barrantes-Vidal, Grant, & Kwapil, 2015).

Schizotypal traits, similarly to schizophrenia, are characterised by a heterogenous cluster of positive (cognitive-perceptual), negative (interpersonal) and cognitive (disorganised) factors (Raine et al., 1994; Barrantes-Vidal et al., 2015). The positive factor denotes the presence of abnormal perceptual experiences (i.e. delusional/paranoid ideation, hallucinations; Arndt, Alliger, & Andreasen, 1991). The negative factor is characterised by social anxiety, blunt affect, etc. The cognitive factor, characterised by odd behaviour and odd speech patterns

(Fossati, Raine, Carretta, Leonardi, & Maffei, 2003; Raynolds, Raine, Mellingen, Venables, & Mednick, 2000).

The presentation associated with high schizotypy traits is qualitatively similar, but less severe than the symptoms found in patients with a schizophrenia-spectrum diagnosis. Namely, studies have reported that similar to patients with schizophrenia, HS individuals present with deficits in cognition and perception (Ettinger, Meyhöfer, Steffens, Wagner, & Koutsouleris, 2014), emotional/social cognition (Phillips & Seidman, 2008) albeit at a less sever or attenuated level. Brain structural and functional abnormalities have also been reported in people with high levels of schizotypy (Ettinger et al., 2014). However, to date, relatively little neuroimaging work has been conducted to assess resting state functional connectivity (RSFC) patterns in high schizotypy. Recent resting state Functional Magnetic Resonance Imaging (rs-fMRI) studies investigating individuals that score highly only on the positive schizotypy subfactor have reported abnormal striatal connectivity (Wang, Ettinger, Meindl, & Chan, 2018), and lower RSFC between ventromedial prefrontal regions and ventral striatal regions; and between the dorsal putamen and the hippocampus (Waltmann et al., 2019). Higher total schizotypy scores (combining positive, negative and cognitive subfactors) have also been associated with lower ventral striatal connectivity (Rössler et al., 2018). However, to date, hippocampal connectivity in individuals with high total schizotypy scores have not been investigated.

In the present study, we used rs-fMRI to examine functional connectivity (FC) in people with low (LS) and high (HS) schizotypal personality traits. Rs-fMRI provides a powerful tool to examine patterns of RSFC in the absence of any task demands by measuring statistical dependencies between spontaneous low frequency fluctuations (in the range 0.01–0.08 Hz) in the blood-oxygen-level-dependent (BOLD) signal (Lee, Smyser, & Shimony, 2013; Rosazza,

Minati, Ghielmetti, Mandelli, & Bruzzone, 2012). The main inference being that, if two regions have high FC then there are, on average, temporal correlations among these areas.

Functional connectivity abnormalities are well established in schizophrenia and high-risk cohorts (see Pettersson-Yeo et al. 2011). This has led to critical insights into the intrinsic neurobiological abnormalities that underlie observed symptoms, whilst providing increasing support for the disconnection hypothesis of the disorder (Friston & Frith, 1995; Friston, Brown, Siemerkus, & Stephan, 2016). The disconnection hypothesis suggests that schizophrenia symptoms arise from abnormal functional integration between distributed brain regions due to altered neuromodulation of synaptic plasticity, particularly in regions of dopaminergic afferents such as medial temporal regions, striatum and prefrontal cortex (Stephan, Baldeweg, & Friston, 2006; Pettersson-Yeo, Allen, Benetti, McGuire, & Mechelli, 2011; Friston & Frith, 1995).

A key connection implicated in altered neuromodulation in schizophrenia is between the hippocampus and the striatum (Allen et al., 2019; Zhou et al., 2008; Lipska, 2004; Meyer-Lindenberg et al., 2005). Decades of neuroimaging work have described anatomical, functional and physiological changes in the hippocampus in schizophrenia patients and in individuals at clinical high risk of developing psychosis (CHR; Schobel et al., 2013; Allen et al., 2012; Mechelli et al., 2011). In turn, increased hippocampal neural activity is believed to lead to the dysregulation of striatal-midbrain dopamine signalling (Lodge & Grace, 2011; Gomes & Grace, 2017) through a hippocampal-striatal-midbrain circuit. Further, longitudinal studies in CHR groups showed that normalization of hippocampal resting cerebral blood flow tracked with clinical improvement of symptoms, while elevated hippocampal resting cerebral blood flow persisted in those who remained symptomatic or developed psychosis (Allen et al., 2016). Studies also report that the hippocampus show reduced FC with distributed brain regions during

rest in schizophrenia (Liang et al., 2006; Zhou et al., 2008) including the bilateral putamen region within the striatum (Kraguljac, White, Hadley, Reid, & Lahti, 2014). Importantly, it has been suggested that the potential behavioural consequence of emerging hippocampal-striatal network dysregulation is aberrant salience processing (Gray, Feldon, Rawlins, Hemsley, & Smith, 1991; Winton-Brown, Fusar-Poli, Ungless, & Howes, 2014). Under abnormally high hippocampal drive of dopamine neuron population activity, the dopaminergic system would be rendered hyper-responsive to phasic stimuli. Under such a state, all stimuli, whether threatening, rewarding, or benign, would cause a maximal phasic activation of the dopamine system (Grace, 2010a; 2010b). As a result, all stimuli would be treated as one that requires maximal attention and reaction; a state that has been termed aberrant salience (Kapur, 2003). The prediction-error signal from the subcortical regions is responsible for 'gating' the access of information to the prefrontal cortex, thus abnormal signalling from subcortical areas is likely to alter prefrontal functional networks and lead to disrupted attention and motivation (as is observed in schizophrenia; Braver & Cohen, 1999). Disrupted prefrontal processing of expectancy violations also correlates with delusion severity in patient samples. In particular, abnormal connectivity has been observed between hippocampus and regions in the prefrontal cortex (PFC), such as dorsolateral PFC and medial PFC (mPFC) in both schizophrenia patients and CHR cohorts (Wolf et al., 2009; Benetti et al., 2009). Previous neuroimaging studies of motivational, reward and novelty salience processing also suggest salience dysregulation and altered activation within a hippocampal–striatal–midbrain network in people at CHR (Gray et al., 1991; Winton-Brown et al., 2017; Roiser et al., 2009; Roiser, Howes, Chaddock, Joyce, & McGuire, 2013; Mondinos et al., 2020). Aberrant salience has also been observed in schizotypy samples (Roiser et al., 2009). Across two experiments testing allocation of attention to cues that have predictive significance, HS individuals demonstrated abolition of the effects of relevance that were otherwise sustained in LS participants (Haselgrove et al., 2016).

Abnormal connectivity between the hippocampus and the thalamus has also been reported in schizophrenia patients (Byne, Hazlett, Buchsbaum, & Kemether, 2009). The midline (i.e. nucleus reuniens) region of the thalamus innervates the hippocampus (Lisman, Pi, Zhang, & Otmakhova, 2010), and the higher basal activity reported in the thalamus in patients with schizophrenia (Malaspina et al., 2004) might lead to the increased hippocampal activity (Allen et al., 2017). Reduced resting state connectivity between the hippocampus and thalamus has also been reported in a large sample of schizophrenia patients compared to controls (Samudra et al., 2015).

Finally, the prefrontal cortex, particularly mPFC, has been reported to show aberrant connectivity in schizophrenia samples, with studies reporting both hypo- and hyper-connectivity patterns (Yu et al., 2012; Zhou et al., 2008; Bluhm et al., 2007, Penner et al., 2016, Zhou et al., 2007; Camchong, McDonald, Bell, Mueller, & Lim, 2011; Chai et al., 2011). Studies exploring models of cognitive control emphasize the interaction between phasic responses in subcortical dopamine neurons and more sustained firing in the prefrontal cortex (Cohen, Braver, & O´ Reilly, 1996; Braver & Cohen, 1999; Miller & Cohen, 2001).

Crucially, to date, previous studies in schizotypy samples have not investigated RSFC between the hippocampus and other key regions implicated in the neuropathology of schizophrenia. Thus, it is unclear if abnormal hippocampal FC, consistently reported in schizophrenia, is present in schizotypy populations. Thus, the aim of the current study was to conduct the first investigations of resting state FC patterns between the hippocampus, striatum, thalamus and prefrontal cortex in a high (relative to a low) schizotypy sample. Based on the importance of hippocampal activity in the progression of psychosis (Allen et al., 2019; Grace, 2016; Lodge & Grace, 2011) we chose the hippocampus as a seed region and examined connectivity patterns with the striatal, thalamic and PFC regions of interest. We predicted that

in the HS group the hippocampus would show reduced FC with the striatum, thalamus and PFC regions. This study also addresses the sample limitations found in previous literature by utilising a cohort that is specifically recruited to test the low vs. high ends of the schizotypy continuum. Using a clearly defined high scoring schizotypy group could serve as a very useful baseline to compare the earliest stages of psychosis risk and draw comparisons between these at-risk samples and schizophrenia populations.

6.2. Methods

6.2.1. Participants

1342 participants (student population, Royal Holloway University of London) responded to an online survey advertised via social media and were pre-screened using the Schizotypy Personality Questionnaire (SPQ; Raine, 1991) and the Marlowe-Crowne Social Desirability Scale (SDS; Fischer & Fick, 1993). Exclusion criteria was defined as: presence of contraindicators for MRI scanning (presence of metal, etc.), current use of prescribed medication for neuropsychiatric disorders or history of neuropsychiatric disorders, current use or history of illicit substances misuse. These criteria were assessed via self-report and pre-screening for MRI scanning. The SDS questionnaire was used to exclude participants that give mainly socially desirable answers (Fischer & Fick, 1993). Subjects who scored 8 or higher (as utilised by previous research; Fischer & Fick, 1993) were excluded.

We recruited the bottom and top 10% deciles of the SPQ distribution, i.e. individuals scoring below 12 and above 41 points on the SPQ (as informed by previous research; SPQ range 0-74, Raine et al., 1994; Raine, 1991). The SPQ provides an overall measure of individual differences in schizotypal personality traits (normally distributed in the general

population; Henry, Bailey, & Rendell, 2008; Kendler et al., 1991) and can be reduced to three latent dimensions (positive, cognitive and negative; Vollema, Sitskoorn, Appels, & Kahn, 2002), mimicking the symptom clusters of schizophrenia and CHR states. We followed the most conventional factor structure to create the three latent subfactors (Raine, 1991). Ideas of reference, magical thinking, unusual perceptual experiences and paranoid ideation loaded on the positive factor; paranoid ideation, social anxiety, no close friends and constricted affect loaded on the negative factor; odd behaviour and odd speech loaded on the cognitive factor (Raine, 1991). The final sample included 27 participants in the HS group (17 females, age range 18-22, 19.25±1.05) and 26 participants in the LS group (19 females, age range 18-27,20.38±2.02).

Ethical approval for the study was obtained from the University of Roehampton's Ethics Committee and all participants provided informed written consent before initiating any study procedures. Participants were compensated for their time (£40 cash payment and a high-resolution anatomical scan of their brain).

6.2.2. Behavioural assessments

On the day of MRI scanning participants completed a validated short version of the Wechsler abbreviated scale of intelligence (WASI II; McCrimmon & Smith, 2013) to assess intellectual ability. Working memory was assessed using the digit span backward task (Dobbs & Rule, 1989). These measures were collected to ensure groups would be matched on key variables. Analysis of demographic and questionnaire data with the effect of group being tested using chi square test or independent samples t-test for parametric data (significance threshold

p < .05) was performed via the statsmodule in Python (https://www.statsmodels.org/stable/index.html).

6.2.3. Imaging acquisition

Scanning was performed on a 3T Siemens Magnetom TIM Trio scanner using a 32-channel head coil at the Combined Universities Brain Imaging Centre. For the rs-fMRI, participants were asked to lie still with their eyes closed, and to think of nothing in particular. Scanning time for the rs-fMRI was 10 min, 300 EPI volumes were collected. During this time, Generalized Autocalibrating Partial Parallel Acquisition (EPI-GRAPPA) images sensitive to BOLD contrast were acquired to measure hemodynamic response (repetition time: 2000 ms; echo time 30 ms; flip angle 70°; 3mm x 3mm x 4.5mm voxel size; field of view 192 mm; 64 x 64 matrix size; 32 axial sections collected with multiband interleaved ascending acquisition; parallel in-plane multiband acceleration factor of 2). No participants were reported sleeping in the scanner. A structural scan was acquired for co-registration of the EPI data by means of a weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MP Rage; repetition time 1900s; 1mm x 1mm x 1mm voxel size; in plane resolution of 256 x 256 x 176 slices, scanning time approximately 5 minutes).

6.2.4. Imaging preprocessing

Images were pre-processed following the recommended pipeline for the analysis of Connectomes (C-PAC; Craddock et al., 2013). The anatomical image was deobliqued using 3drefit in the Analysis of Functional NeuroImages (AFNI) framework

(https://afni.nimh.nih.gov) and reoriented into RPI using AFNI's 3dresample. Skull stripping was performed with AFNI's 3dSkullStrip. FSL FLIRT was used to perform a linear transformation of the skull stripped image into 2mm Montreal Neurological Institute (MNI) template space (Jenkinson, Bannister, Brady, & Smith, 2002). The registration was then refined using non-linear transformation performed by FSL FNIRT (Andersson, Jenkinson, & Smith, 2007). The skull stripped normalised T1 was segmented using FSL FAST (Zhang, Brady, & Smith, 2001). Tissue masks for the cerebrospinal fluid (CSF), white matter(WM) and grey matter (GM) were created using FSL and the following procedure: registering the tissue template in MNI space to native space using FSL prior tissue probability maps, finding overlap between the tissue probability maps and the tissue template created in the previous step, applying a 0.4 threshold and binarizing the tissue templates (Craddock et al., 2013), and finally generating the tissue masks by applying the prior in native space to the binarized tissue probability map.

The EPI images were deobliqued and reoriented into RPI using AFNI, and slice time correction was performed with AFNI's 3dTshift. AFNI's 3dTstat was used to obtain mean intensity values over all timepoints for each voxel (base image). Two pass motion correction was performed on the data using AFNI's 3dvolreg. For each volume the image was aligned with the base mean image, providing motion displacement and movement parameters. Voxel wise statistics for the motion corrected output from this step were used as the base for the second pass motion correction using 3dvolreg and a Fourier transformation to obtain the motion and displacement parameters. The images were registered to the subject's T1 scan using FLIRT (linear transformation), and subsequently normalised to MNI space. The normalized images were smoothed with AFNI's 3dmerge using a 6mm FWHM kernel (Miki et al., 2008). Nuisance regression to remove noise signals from the data was performed using AFNI's 3dDeconvolve and 3dTproject. For this step, the motion parameters were demeaned, and motion parameter

derivatives were calculated. The CSF and WM masks were resampled into functional space using AFNI's 3dresample and respective time courses were extracted. The demeaned 6 motion parameters, the 6 motion derivatives and the CSF and WM signal were regressed out of the data and the low bandpass filter (frequency range 0.01-0.1 Hz) were applied in AFNI. Subjects with motion exceeding 3mm and/or mean framewise displacement exceeding the 0.5mm threshold (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012) were removed from the sample, resulting in a total sample of 22 participants in the HS group and 23 participants in the LS group. A comparison of the mean framewise displacement (FD; Power et. al., 2012) between the final HS (0.32±1.2) and LS groups (0.25±1.7) revealed no significant difference in head motion between the groups ($t = 0.41$, $p = 0.68$).

6.2.5. Imaging analysis

The bilateral 5mm spherical hippocampus seed region (± 27, -15, -19; Fig 1) was identified by using the Harvard-Oxford cortical and subcortical structural atlases in FSL (Goldstein et al., 2007). The seed was placed in the bilateral anterior hippocampus, as these regions are closely connected with subcortical areas and the mPFC (Heckers & Konradi, 2010) and have been linked to altered function in schizophrenia (Schobel et al., 2013). Furthermore, in CHR samples reductions in volume and altered function have been localized to the anterior part of the hippocampus (Schobel et al., 2013; Grace 2010b, Grace 2016).

These masks were resampled in functional space using AFNI's 3dresample. The binarized bilateral anatomical masks used for our a-priori regions of interest (ROIs) to investigate connectivity at the group level were created using the same atlases in FSL and were as follows: ventral striatum (± 10, 12, -6, k voxels 1582), caudate (± 9, 11, 7, k voxels = 901),

putamen (± 24, 11, -2, k voxels = 901), thalamus (± 14, -24, 6, k voxels = 2268), mPFC (including the dlPFC; ± 40, 28, 37, k voxels = 3993) and vmPFC (± 14, 41, -14, k voxels = 4160). For each subject, a dual regression in FSL was performed at the first level of analysis to simultaneously extract the time series and calculate the seed-based correlations between the hippocampal seed's time-series and the rest of the brain (voxel-wise; Nickerson, Smith, Öngür, & Beckmann, 2017).

The resulting images were taken to group-level analysis using FSL's randomise (Winkler, Ridgway, Webster, Smith, & Nichols, 2014). For every connectivity analysis we performed nonparametric inferential statistics with 10000 permutations per analysis using the threshold free cluster enhancement (TFCE) method for defining clusters and the respective anatomical mask to define connectivity between hypothesized regions of interest. Connectivity differences between groups were examined via two sample t-test in FSL's General Linear Model (GLM). Results are reported at a voxel-wise correction for multiple testing at $p < 0.05$ family-wise error (FWE) rate. Where we observed group differences in resting state functional connectivity (RSFC), we conducted separate GLM models with the schizotypy subfactor scores (positive, negative, cognitive) entered as continuous regressors to investigate which subfactor scores were driving group effect (i.e. same seed and anatomical ROI, but subfactor not group regressors).

6.3. Results

6.3.1. Demographics and questionnaires

Table 1 summarizes the sociodemographic characteristics by group. HS and LS groups were matched for gender, age and IQ but differed on all schizotypy measures due to design.

Table 1. Demographic and questionnaire data across LS and HS groups.

Characteristic	LS (n = 23)	HS (n=22)	t/χ2	p
Gender(male/female)	6/17	8/14	0.55	0.45
Age (years)	20.13 (SD = 2.10)	19.45(SD= 1.05)	1.09	0.27
WASI II IQ	94.43(SD = 9.20	92.68 (SD = 9.26)	0.63	0.52
Digit Span Score	4.43 (SD = 1.07)	4.09 (SD = 0.75)	1.23	0.23
SDS	5.96 (SD = 1.52)	4.86 (SD = 2.33)	1.86	0.07
SPQ Total	7.61 (SD = 3.60)	46.64 (SD = 5.23)	-29.25	< 0.01
SPQ Positive Factor	2.83 (SD= 2.01)	20.41 (SD = 5.22)	-15.02	< 0.01
SPQ Negative Factor	3.57 (SD = 2.48)	20.86 (SD = 4.44)	-16.22	< 0.01
SPQ Cognitive Factor	1.91 (SD = 2.42)	10.77 (SD = 2.82)	-11.29	< 0.01

LS – Low Schizotypy; HS – High Schizotypy; SPQ – Schizotypy Personality Questionnaire.

6.3.2. Rs-fMRI results

Relative to LS group, the HS groups showed reduced RSFC between the hippocampus and the left dorsocaudal putamen (voxel-wise TFCE $p_{FWE} = 0.02$), the right caudate (voxel-wise TFCE $p_{FWE} = 0.031$) and the left thalamus (voxel-wise TFCE $p_{FWE} = 0.04$) (Table 2, Fig 1). There were no group differences observed for prefrontal regions and there were no regions that showed reduced FC in the LS relative to the HS group. Exploratory whole brain group analyses were non-significant.

Table 2. Differences in values for resting state fMRI hippocampal connectivity between high and low schizotypy.

Direction	Area	Side	MNI coordinates			Z-value	K_E	P_{FWE}
			x	y	z			voxel
LS > HS	Caudate	Right	16	-16	21	4.59	17	0.03
	DCP	Left	-28	-18	4	2.55	36	0.02
	Thalamus	Left	-20	-20	6	3.55	98	0.04

LS – Low Schizotypy; HS – High Schizotypy, DCP – dorsocaudal putamen

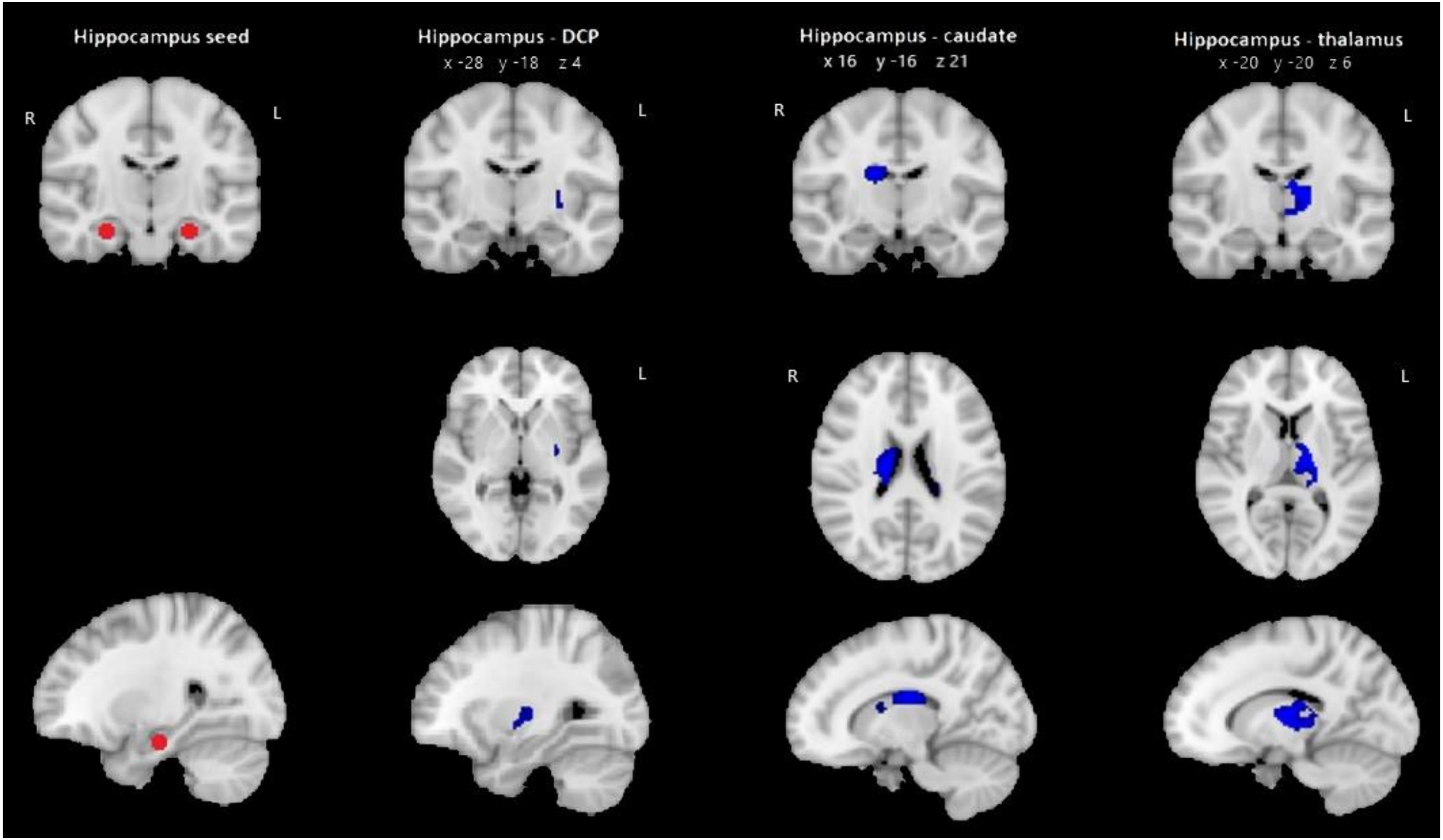


Fig 1. Seed location (in red) and voxels showing significant reduced FC patterns in HS vs LS subjects (in blue). Caudate effect is seen on the right side, DCP and thalamus effect is seen on the left side. DCP - dorsocaudal putamen. Coordinates are in MNI space.

To investigate the effects of each subfactor on the observed abnormal seed-ROI connectivity pattern, we carried out another 3 GLMs with schizotypy subfactors (positive, negative, cognitive) as regressors. The positive subfactor of SPQ showed a significant positive effect with the hippocampus – caudate and hippocampus – thalamus connectivity at a Bonferroni corrected level, results are summarised in Table 3 and Fig 2. The negative and cognitive subfactors had predominantly negative effects on the hippocampal RSFC across the sample but these effects did not survive Bonferroni correction. Connectivity parameter estimates that reached significance for the positive subfactor were extracted from caudate and thalamic ROIs and submitted to independent sample t-tests to check for group differences (LS vs. HS). Hippocampus-thalamus connectivity was significantly greater in HS compared to the LS group, $t = 1.81$, $p = 0.04$. Hippocampus-caudate connectivity was also significantly greater in the HS compared to the LS group, $t = 2.95$, $p < 0.01$, suggesting that the HS group are driving these connectivity patterns (Fig 3).

Table 3. Effects of SPQ subfactors on hippocampal connectivity.

Direction	Area	Side	MNI coordinates			Z-value	K_E	P_{FWE}
			x	y	z			voxel
↑ SPQ P	Caudate	Right	18	-10	24	3.79	12	0.02*
↓ SPQ N	Caudate	Right	17	-11	11			0.1
↓ SPQ C	Caudate	Right	17	-10	23			0.2
↑ SPQ P	DCP	Left	-30	-15	3			0.1

↑ SPQ N	DCP	Left	-28	-10	-1			0.1
↓ SPQ C	DCP	Left	-30	-9	-3			0.2
↑ SPQ P	Thalamus	Left	-2	-18	10	3.9	17	0.02 *
↓ SPQ N	Thalamus	Left	-2	-16	10			0.07
↓ SPQ C	Thalamus	Left	-8	-24	7			0.1

** Bonferroni corrected*
↑ Positive effect; ↓ Negative effect
P – Positive Factor, N– Negative Factor, C – Cognitive Factor
SPQ – Schizotypy Personality Questionnaire, DCP – dorsocaudal putamen

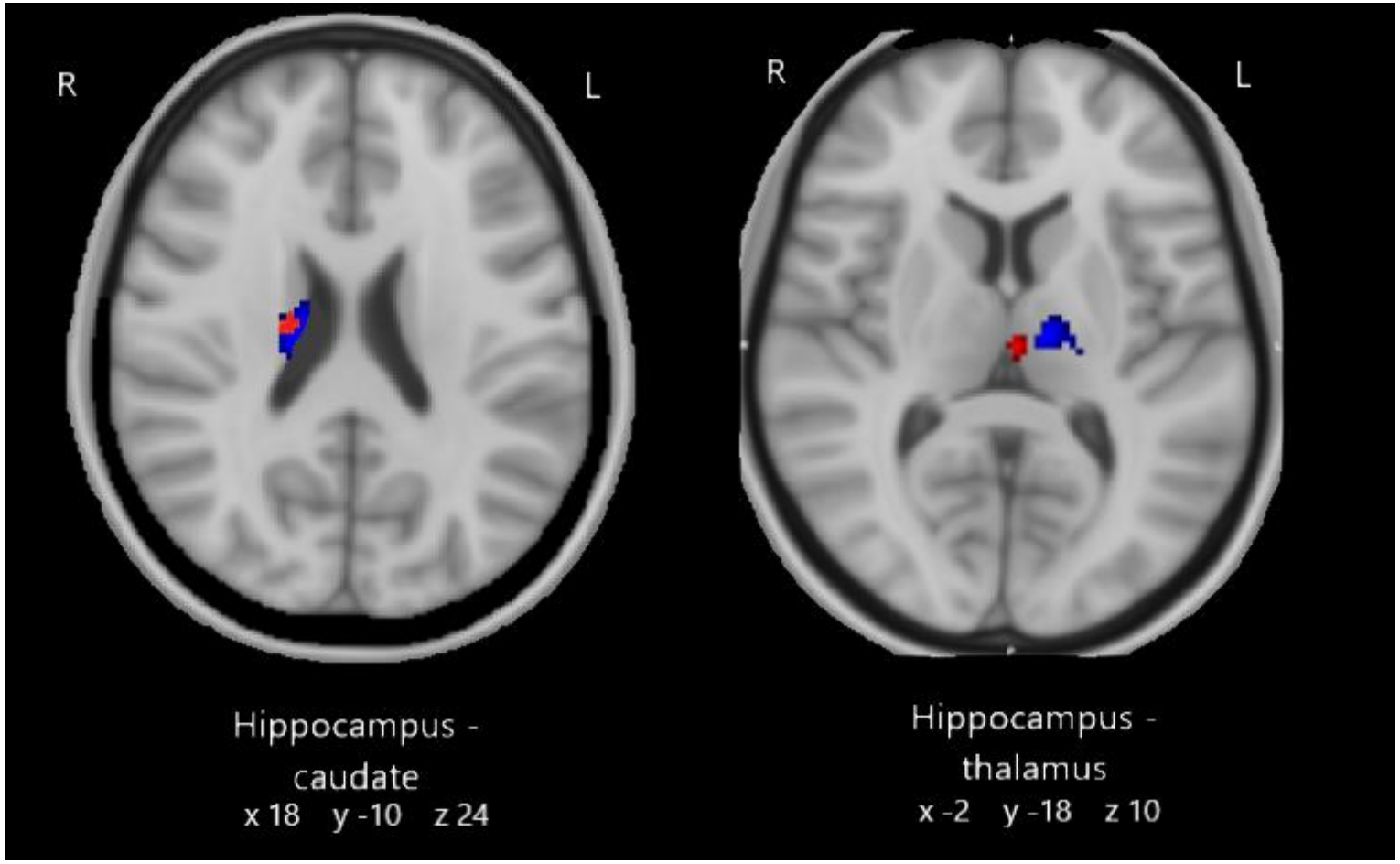
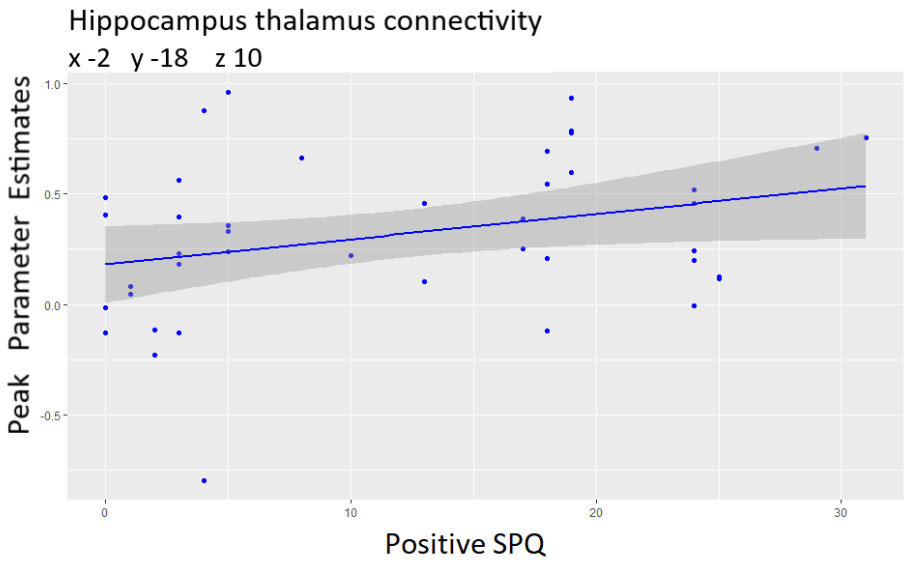
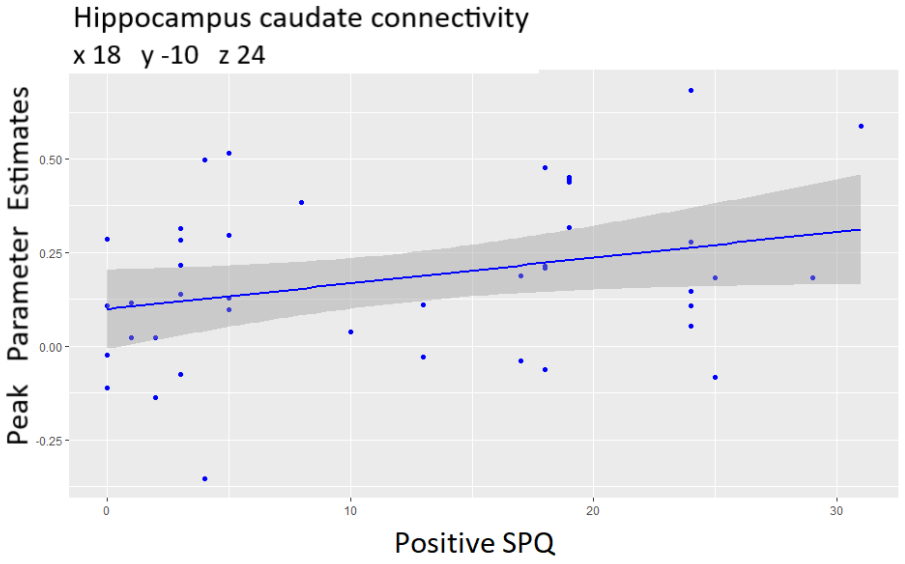
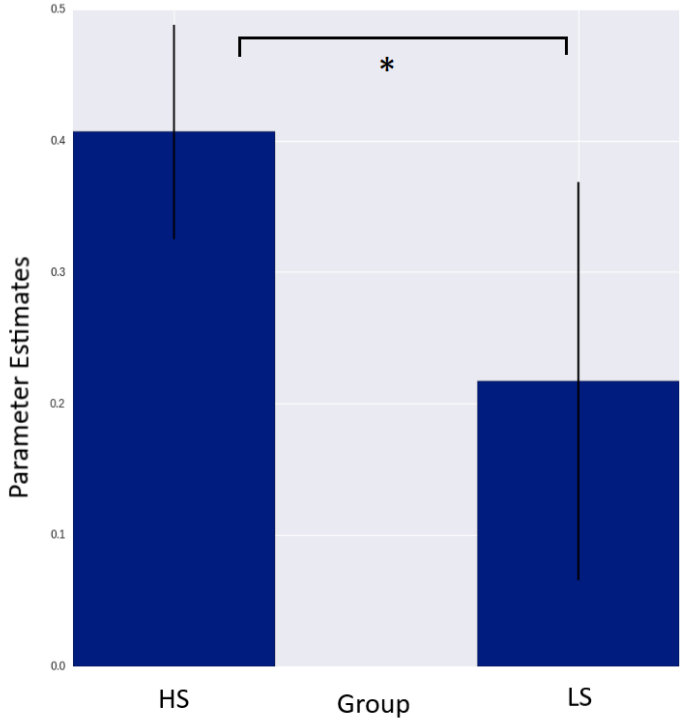


Fig 2. Brain maps for significant positive connectivity between SPQ CP and hippocampus – caudate (left panel) and hippocampus – thalamus (right panel). Red represents the significant peak activation for SPQ CP, for comparison blue represents the peak activations observed for LS > HS connectivity from the previous analysis. Coordinates are in MNI space.


Hippocampus thalamus connectivity
x -2 y -18 z 10
Peak Parameter Estimates
Positive SPQ


Hippocampus caudate connectivity
x 18 y -10 z 24
Peak Parameter Estimates
Positive SPQ


*
Parameter Estimates
HS
Group
LS

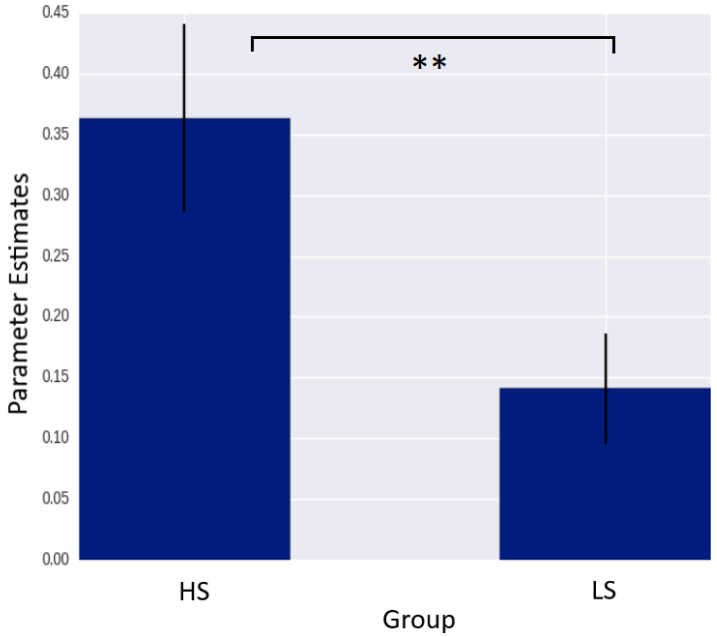

**
Parameter Estimates
HS
Group
LS

Fig 3. Top row. Connectivity patterns between positive SPQ (x-axis) and peak parameter estimates for the hippocampus-thalamus and hippocampus-caudate connectivity, respectively (y-axis). Coordinates are given in MNI space. Bottom row. Bar plots shows connectivity parameters estimates (for positive subfactor analysis) in thalamic and caudate ROI (error bars represent standard deviations) for LS and HS groups. * - p significant at 0.05, ** - p significant at 0.01.

6.4. Discussion

The present study shows reduced RSFC between the hippocampus and striatum and between hippocampus and thalamic regions (mainly the mediodorsal nucleus and midline thalamic nucleus) in HS relative to LS participants. However, the HS and LS groups showed no difference in hippocampal – PFC connectivity. These findings suggest that abnormal hippocampal FC is characteristic of high schizotypy. The subfactor analysis shows that, whilst lower RSFC in HS subjects is driven by total schizotypy scores, the positive schizotypy factor showed a positive correlation with hippocampus-caudate and hippocampus-thalamus connectivity. Extraction of the peak parameter estimates showed that the association between functional connectivity and positive SPQ scores is significantly higher in the HS compared to the LS group.

The finding of reduced functional connectivity between the hippocampus and other regions in the HS group is in line with previous research that implicates hippocampal disfunction and connectivity in the emergence of psychosis (Allen et al., 2015; Grace, 2010b; Grace, 2016) and in established schizophrenia (Samudra et al., 2015; Kraguljac et al., 2016; Kraguljac et al., 2014; Zhou et al., 2008) and provides support for the disconnectivity hypothesis of the disorder (Stephan, Friston, & Frith, 2009; Bullmore, Frangou, & Murray, 1997; Andreasen, Paradiso, & O'leary, 1998). Taken together, current and previous findings are in line with the broader schizophrenia literature and suggest that psychosis risk cohorts present with similar abnormal neural signatures in medial temporal regions as those seen in clinical samples. However, we did not observe changes in hippocampal – PFC connectivity, a finding that has been reported previously in schizophrenia (Yu et al., 2012; Zhou et al., 2008; Bluhm et al., 2007, Penner et al., 2016) and psychosis risk cohorts (Benetti et al, 2009).

The current findings are also broadly consistent with animal models of psychosis development that propose hippocampal dysfunction and disconnectivity results in perturbed striatal dopamine signalling (Howes et al., 2009; Modinos, Allen, Grace, & McGuire, 2015). In humans there is significant literature demonstrating schizophrenia and CHR cohorts present with increased hippocampal resting activity and perfusion, specifically increased regional cerebral blood flow and increased regional cerebral blood volume (Allen et al., 2017; Allen et al., 2015; Tamminga, Stan, & Wagner, 2010; Hackers et al., 1998; Schobel et al., 2009; Medoff, Holcomb, Lahti, & Tamminga, 2001). According to rodent models, a consequence of hippocampal hyperactivity and altered hippocampal-striatal connectivity (Modinos et al. 2020; Winton-Brown et al., 2017) is a sustained increase in extrasynaptic dopamine release throughout midbrain and striatal regions (Peleg-Raibstein & Feldon, 2006; Blaha, Yang, Floresco, Barr, & Phillips, 1997; Legault & Wise, 1999). However, few studies have directly examined connectivity between hippocampal and striatal regions in psychosis risk groups, and none in a high schizotypy sample.

Interestingly, when considering positive schizotypy traits in the current study, hippocampal-striatal connectivity was increased in HS relative to LS groups. Findings from our subfactor analysis are broadly consistent with a recent study in a CHR cohort (operationally defined using positive symptom criteria) that reports increased effective connectivity between the hippocampus and the striatum in CHR participants relative to healthy controls (Modinos et al., 2020). The SPQ positive subscale includes items assessing abnormal and delusional beliefs. According to rodent models of psychosis (Lodge and Grace 2011; Modinos et al., 2015), increased hippocampal – striatal signalling may lead to dysregulation of striatal dopamine function and aberrant salience, a behavioural construct that has been observed in schizophrenia (Kapur 2003, White, Joseph, Francis, & Liddle., 2010), psychosis risk (Roiser et al., 2013, Howes et al., 2020) and schizotypy samples (Roiser et al., 2009; Haselgrove et al. 2016) and is

thought to underpin delusional belief formation (Kapur, 2003). However, in the current study it is not possible to confirm if the hippocampal-striatal abnormal connectivity is associated with abnormal dopamine signalling as no direct measures of this process were acquired. Indeed, striatal dopamine activity in schizotypy has scarcely been investigated, although existing research suggests that individuals with high levels of schizotypy may benefit from DA agonists in terms of cognitive performance (Mohr & Ettinger, 2014). Future multimodal neuroimaging studies employing Positron Emission Tomography will be needed to examine if altered hippocampal – striatum connectivity observed here in HS subjects is related to abnormal dopamine function.

As hypothesized, we also observed reduced RSFC between the hippocampal seed region and the thalamus, mainly in the midline thalamic nucleus but also spanning other thalamic nuclei. The midline thalamic nucleus specifically innervates the CA1 region of the hippocampus (Vertes et al. 2006) and could be a possible source of the observed increased hippocampal activity in schizophrenia (Allen et al., 2015; Schobel et al., 2009). Studies reveal less regional metabolic activity in the thalamus of schizophrenia patients compared to controls (Clark, Kopala, Li, & Hurwitz, 2001; Hazlett et al., 2004) and several studies have reported reduced volume of the thalamus in both patients (Ettinger et al., 2001) and schizotypy samples (Byne et al., 2001; Siever et al., 2002). Our findings contribute to the growing literature suggesting that the connectivity (and functioning; Siever et al., 2002) of the thalamus is related not only to schizophrenia but also to psychometrically identified schizotypal personality traits of healthy individuals.

Our hypothesis that HS subjects would show altered connectivity between the hippocampus and PFC was not supported by our findings. Abnormal functional connectivity of the PFC has been reported in schizophrenia samples (with most seed-based analyses

reporting decreased connectivity; Yu et al., 2012; Zhou et al., 2008; Bluhm et al., 2007; Zhou et al., 2007; Camchong et al., 2011; Chai et al., 2011; Penner et al., 2016; Anticevic et al., 2015), in CHR cohorts (Benetti et al., 2009) and in schizotypy samples (Zhang et al., 2014; Wang et al., 2018). The failure to replicate this finding here could be due to the selection of the hippocampus seed, as previous schizotypy studies reported abnormal PFC connectivity in mainly striatal or limbic areas. Another possibility is that hippocampal-striatal abnormalities occur early in psychosis, whereas frontal-temporal dysconnectivity occurs later in the trajectory (Allen et al., 2019). Indeed, studies of clinical high-risk populations have shown that hippocampal volume, function and perfusion changes can predict conversion to psychosis (Schobel et al., 2013; Allen et al., 2012; Mechelli et al., 2011). In comparison, there is no clear neuroimaging evidence that frontal-temporal connectivity/function is a robust predictor of conversion to psychosis. Furthermore, schizotypal individuals do not appear to show the volumetric decreases in frontal cortex that schizophrenic patients evidence (Siever et al., 2002).

Finally, our results suggest that hippocampal hypoconnectivity with the striatum and the thalamus are characteristic of combinations of schizotypy factors and not a specific subfactor alone. These findings are in line with previous studies reporting that combining indices of schizotypal psychometric components, rather than specific separate symptom clusters, best predict progression to a psychosis disorder (Miller et al, 2002; Mason et al., 2004). Analysis of the effects of subfactors on connectivity suggest that the hypoconnectivity observed in HS, compared to LS, is driven by the negative and cognitive subfactors of SPQ, although these effects did not survive correction for multiple tests. Conversely, the positive dimension of SPQ showed a significant positive association with hippocampal connectivity within the caudate and thalamus across the sample. The opposite effects seen for positive SPQ scores suggest this dimension maybe phenotypically different from the other two subfactors. The positive correlation between positive SPQ and hippocampal caudate/thalamus connectivity

is in line with animal models of psychosis which show that increased hippocampal neural activity leads to the dysregulation of striatal-midbrain dopamine signalling through a hippocampal-striatal-midbrain circuit (Lodge & Grace, 2011; Gomes & Grace, 2017). There has been research in schizophrenia patients suggesting that the striatum is more sensitive to levels of positive symptoms, with findings showing that baseline positive symptoms are associated with more striatal volume loss over time (Ebdrup, 2011). Our results match well with animal models indicating the increasing positive traits lead to increasing hippocampal connectivity within a midbrain-thalamus circuit. Yet, a combination of high positive, negative and cognitive SPQ scores lead to reduced connectivity within these circuits. Recent systematic work has concluded that the positive schizotypy dimension is mainly associated with the later emergence of psychotic disorders, while the negative dimension is selectively associated with the emergence of non-psychotic schizophrenia-spectrum diagnoses (i.e. schizotypal disorder; Debbané et al., 2015). Altogether results suggest that in psychosis high-risk research, schizotypy should not be reduced to its positive dimension but assessed multidimensionally to enable comprehensive risk assessment.

The current findings need to be considered in light of present limitations. We could not test the link between hippocampal connectivity and striatal dopaminergic function. To our knowledge, no longitudinal studies have investigated neural or dopamine factors in high schizotypy individuals and if these can predict later transition to psychosis. Longitudinal neuroimaging studies utilising CHR samples report that transition to psychosis is linked to progressive increases in subcortical dopamine function (Howes et al., 2011). Additionally, the subgroups that go on to develop psychosis show elevated presynaptic dopamine synthesis (Howes et al., 2009). Similar investigations in schizotypy samples would provide crucial evidence regarding the similarities and differences across the spectrum, yielding clues as to the potential determinants of psychosis risk and occurrence of symptoms.

In conclusion, using seed-based analysis in rs-fMRI we found that HS, in comparison to LS individuals, showed reduced FC between hippocampus and striatum and between hippocampus and thalamus, and these differences were characteristic of total schizotypy. Furthermore, increasing positive SPQ traits were associated with increased hippocampal RSFC. Given that the hippocampus has been widely implicated in pathophysiological models of psychosis development, and preliminary findings suggest that connections between hippocampus and striatum might be aberrant in schizotypy (similar to abnormalities observed in CHR populations) the current findings provide further support for the dysconnectivity hypotheses of schizophrenia. Furthermore, the current work supports the conclusion that schizotypy is a valuable methodological population to study the extended psychosis spectrum in order to gain further insight into abnormalities relevant to transition to clinical symptoms.

Chapter Seven

Reduced cortical GABA and glutamate in high schizotypy

Abstract

Abnormal functioning of the inhibitory gamma-Aminobutyric acid (GABA) and excitatory (glutamate) systems is proposed to play a critical role in the development of schizophrenia-spectrum disorder, as evidenced by animal and post-mortem studies. Previous human Magnetic Resonance Spectroscopy (MRS) studies in schizophrenia and clinical high-risk samples are consistent with pre-clinical work showing these metabolites are altered in comparison to healthy controls. Whether or not GABA and glutamate metabolite concentrations are altered in people with high schizotypy traits remains to be investigated. The current study utilises MRS to examine GABA and glutamate levels from a voxel in the medial prefrontal cortex in people with low (n for GABA = 19, n for glutamate = 26) and high (n for GABA = 19, n for glutamate = 25) schizotypy traits as assessed with the Schizotypy Personality Questionnaire. Compared to individuals with low schizotypy traits, high schizotypy individuals showed significantly lower cortical GABA and glutamate metabolite levels. Furthermore, the ability to cope with stress (i.e. resilience) interacted with GABA levels, to predict schizotypy group membership (low versus high). These findings demonstrate that subclinical schizotypal traits are associated with abnormal functioning of both inhibitory and excitatory systems and suggest that these transmitters may be implicated in risk for the development of psychosis.

7.1. Introduction

There is a growing consensus that psychosis exists on a continuum ranging from subclinical psychotic-like experiences in the general population to full-blown psychotic symptoms in clinical samples (Linscott & Van Os, 2013). Psychotic-like experiences in healthy people, commonly referred to as schizotypy, represent a latent personality organization reflecting an underlying vulnerability to developing schizophrenia-spectrum disorders (Barrantes-Vidal, Grant & Kwapil, 2014). Thus, investigating schizotypal traits in non-clinical samples may inform us on aetiological mechanisms underlying risk for psychosis.

The presentation of high schizotypal traits is qualitatively similar, but less severe than the symptoms found in schizophrenia. Relative to patients with schizophrenia, individuals scoring high on schizotypy traits measures present with similar (albeit weaker) deficits in cognition and perception. High schizotypy has also been linked with brain structural and functional abnormalities relative to control groups (Ettinger, Mayhofer, Steffens, Wagner & Koutsouleris, 2014). However, fewer studies have investigated if there are neurochemical alterations in schizotypy populations similar to those reported in schizophrenia (Egerton, Modinos, Ferrera & McGuire, 2017) and in psychosis risk cohorts (Du & Grace, 2013).

Whilst several studies have investigated changes in dopaminergic functions in schizophrenia samples (Du & Grace, 2013; Grace, 2010; Goto & Grace, 2006) to date, there only have been few studies of GABAergic and/or glutamate function in schizotypy populations. The investigation of GABAergic and glutamatergic function is important because evidence from animal models and post-mortem studies of psychosis suggest that dysregulated excitatory and inhibitory neurotransmission plays an important role in the development of schizophrenia-like symptoms (Du & Grace, 2013; Grace, 2010; Goto & Grace, 2006). The pre-clinical

methylazoxymethanol acetate (MAM) rodent model of psychosis shows reduced parvalbumin expression in MAM treated rats that may be linked to schizophrenia-like pathology (Gastambide et al., 2012). In particular, reduced parvalbumin expression may impact on prefrontal cortex (PFC) GABAergic interneurons, that are known to be decreased in schizophrenia populations (Akbarian et al., 1995; Lewis, Hashimoto & Volk, 2005). The MAM model also proposes dysfunction of the glutamatergic system as a possible mechanism increasing risk for psychosis (Marsman et al., 2013). The glutamatergic system is believed to affect synaptic plasticity and cortical microcircuitry, in particular (N-methyl-D-aspartate) NMDA-receptor signalling (Merritt, Egerton, Kempton, Taylor & McGuire, 2016). Furthermore, the MAM model of psychosis emphasise a link between disrupted GABAergic and glutamatergic function and dysregulation of subcortical dopaminergic signalling (Grace, 2010).

Consistent with pre-clinical work, studies in human subjects with a diagnosis of schizophrenia or with a clinical high-risk state (Marsman et al., 2013; Merritt et al., 2016) report altered GABAergic and glutamatergic function relative to healthy control groups across a range of cortical and subcortical regions. Moreover, pharmacological challenge studies in humans report that the administration of NMDA-receptor antagonists, such as ketamine and phencyclidine (PCP), induce symptoms that mimic the positive and negative symptoms seen in schizophrenia (Harrison & Weinberger, 2005; Krystal et al., 1994; Moghaddam, Adams, Verma & Daly, 1997).

Crucially however, studies investigating GABA and glutamate metabolite concentrations in high schizotypy samples are limited. Such studies are important if we are to better understand the role of (perturbed) inhibitory and excitatory neurotransmission in psychosis risk and associated phenotypes. One previous study investigating glutamate levels

in individuals with high positive schizotypy traits reported no differences in metabolite concentrations levels in the anterior cingulate cortex relative to a low positive schizotypy control group. There was however an interaction effect such that glutamate levels were negatively associated with the degree of cortical activation in response to emotional pictures in the striatum and the mPFC (Modinos et al., 2017). These preliminary findings suggest that cortical glutamate levels might be perturbed in high (positive) schizotypy in the context of affective function.

Given the paucity of MRS studies in schizotypy populations, in the current study we sought to investigate GABA and glutamate metabolite concentrations in a sample of high schizotypy participants, relative to a low schizotypy control group. We used MRS with a voxel located in the medial PFC as pre-clinical models implicate this region in the neuropathology of psychosis and psychosis risk. Moreover, a number of previous MRS studies in CHR and schizophrenia samples have investigated this region and reported altered metabolite concentrations in the mPFC (Becker et al., 2003; Modinos et al., 2017; Mailly, Aliane, Groenewegen, Haber & Deniau, 2013). Given that MRS studies in schizophrenia cohorts have reported both increased and decreased GABA and glutamate metabolite concentrations in prefrontal regions (Marsman et al., 2013; Merritt et al., 2016), we predicted that relative to low schizotypy participants, high schizotypy participants will show altered GABA and glutamate metabolite concentration in the mPFC.

Finally, animal models of schizophrenia indicate that inhibitory and excitatory neurotransmitter system are strongly influenced by environmental stress, particularly during development (Zhang et al., 2010; Guidotti et al., 2011). In line with findings implicating stress in the development of psychosis (Corcoran, Walker, Huot, Mittal & Tessnek, 2003), it has been suggested that individuals with high schizotypy and low resilience (ability to cope with stress)

have a greater risk of progress to a schizophrenia-spectrum clinical diagnoses (Barrantes-Vidal et al., 2014). To investigate the role of stress/resilience in relationship between schizotypy and GABA and glutamate concentrations, we also included a psychometric measure of resilience.

7.2. Methods

7.2.1. Participants

1342 participants responded to an online survey advertised via social media and were pre-screened using the Schizotypy Personality Questionnaire (SPQ; Raine, 1991) and the Marlowe-Crowne Social Desirability Scale (SDS; Fischer & Fick, 1993). All participants that took part in the MRI study were recruited from the student population of the Royal Holloway University of London. Exclusion criteria was defined as presence of contraindicators for MRI scanning (presence of metal, etc.), current use of prescribed medication for neuropsychiatric disorders or history of neuropsychiatric disorders, current use or history of illicit substances misuse. These criteria were assessed via self-report and pre-screening for MRI scanning. The SDS questionnaire was used to exclude participants that give mainly socially desirable answers, thus only subjects scoring 8 or higher on this measure were excluded to control for socially desirable responding (Fischer & Fick, 1993).

Subjects were invited to take part in the study based on their SPQ score. The aim of the study was to recruit the bottom and top 10% (decilles) of the schizotypy continuum (SPQ distribution) thus individuals scoring below 12 and above 41 points on the SPQ were invited to take part (as informed by previous research; Raine, 1991). The SPQ provides an overall measure of individual differences in schizotypal personality traits and can be reduced to three

latent dimensions (positive, disorganised and negative; Raine, 1991), mimicking the symptom clusters of schizophrenia and clinical high-risk states. The final sample included 27 participants in the high schizotypy group (HS; 17 females, age range 18-22, M = 19.25, SD = 1.05) and 26 participants in the low schizotypy group (LS; 19 females, age range 18-27, M = 20.38, SD = 2.02).

Ethical approval for the study was obtained from the University of Roehampton's Ethics Committee and all participants provided informed written consent before initiating any study procedures. Participants were compensated for their time (£40 cash payment and a high-resolution anatomical scan of their brain).

Participants also completed demographic and substance use measures and the 25-item Connor-Davidson Resilience Scale (CD-RISC; Campbell-Sills & Stein, 2007) to measure their resilience levels. The CD-RISC scale was developed to measure the ability to cope with adversity, with higher scores indicating greater resilience. Higher CD-RISC scores indicate higher levels of resilience and an increased ability to cope with stress (Campbell-Sills & Stein, 2007). On the day of MRI scanning participants completed a validated short version of the Wechsler abbreviated scale of intelligence (WASI II) to assess intellectual ability (IQ).

7.2.2. MRI acquisition

All MRI scans were acquired on a 3T Siemens Magnetom TIM Trio scanner using a 32-channel head coil. Structural T1 weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MP RAGE) images were acquired with a spatial resolution of 1 mm × 1 mm × 1 mm, in plane resolution of 256 × 256 × 176 slices and scanning time of approximately 5 minutes. T1 MP RAGE scans were acquired for localization of the spectroscopy voxel

placement and were subsequently segmented into tissue maps to allow volume correction for grey and white matter as well as CSF within the mPFC voxel, i.e. partial volume tissue contamination.

7.2.3. 1H-MRS data acquisition and analysis

1H-MRS in vivo spectra were acquired from a 20 × 20 × 20 mm voxel located in the bilateral medial PFC during rest (Fig 1). The reasoning for choosing a medial PFC position was two-fold. First, lateral voxels can be harder to place due to tissue boundaries. Second, the medial PFC has shown abnormal GABA levels in schizophrenia patients in a number of previous studies and is one of the most commonly used MRS voxel placements for psychosis populations (Egerton et al., 2017; Modinos et al., 2017; Stone et al., 2009).

The voxel was positioned manually by reference to an axial T1-weighted gradient echo image (Fig 1). Spectra were acquired using Spin Echo full Intensity-Acquired Localized spectroscopy (SPECIAL; Mlynárik, Gambarota, Frenkel, & Gruetter, 2006). 1H-MRS sequence was acquired with water suppression (TR 3000 msec, TE 8.5 msec, phase cycle auto, 192 averages from the right PFC voxel) in each participant (Godlewska, Near & Cowen, 2015). Water unsuppressed spectra (16 averages) were also acquired. Six outer volume suppression slabs were applied (one on each side at 5 mm from the edge of the cubic voxel) to suppress signals originating from outside the volume of interest and to minimize motion-related image-selected in vivo spectroscopy subtraction artefacts. Spectra were analysed using LCModel 6.3-1N with the basis set consisting of 19 simulated basis spectra; alanine (Ala), ascorbate (Asc), aspartate (Asp), creatine (Cr), γ-aminobutyric acid (GABA), glucose (Glc), glutamine (Gln), glutamate (Glu), glycine (Gly), glutathione (GSH), glycerophosphocholine (GPC) phosphocholine (PCh), lactate (Lac), myo-inositol (mI), N-acetylaspartate (NAA), N-

acetylaspartateglutamate (NAAG), phosphorylethanolamine (PE), scyllo-inositol (Scyllo) & taurine (Tau).

The basis set was simulated using FID-A (Simpson, Devenvi, Jezzard, Hennnessy & Near, 2017) for TE = 8.5 msec, magnetic field strength = 3 T and assuming ideal RF pulses. We excluded spectra with Cramer-Rao lower bounds (CRLB) > 20% as reported by LCModel. Line widths and signal-to-noise ratios were calculated by LCModel for both LS and HS groups (see Results). All spectra had a Line Width <8 Hz and an SNR >40 (Godlewska et al., 2015). Following these quality control checks 8 participants from the HS group and 5 participants from the LS group were excluded due to CLRB ratios for GABA > 20%. Thus, the reported results for GABA are from 40 subjects in total (19 HS and 21 LS). For analysis of glutamate, quality control checks indicated that 2 subjects from the HS group had to be excluded due to CLRB ratios for Glu > 20%, resulting in a total sample of 25 HS and 26 LS individuals from the analysis of glutamate.

Metabolite levels have been shown to depend on the amount of cerebral spinal fluid (CSF), gray (GM) and white matter (WM) within the voxel (Srinivasn et al., 2006), and inter-individual differences in cortical gray matter (Huster, Westerhausen, Kreuder, Schweiger, & Wittling, 2007). To account for these confounds we used the T1-weighted anatomical images to estimate the gray and white matter content of the mPFC voxel in which the 1H-MRS measures were acquired using FSL FAST segmentation (Zhang, Brady & Smith, 2001). For every subject, tissue masks for CSF, GM and WM were created using FSL and the following procedure: registering the tissue template in MNI space to native space using FSL prior tissue probability maps, finding overlap between the tissue probability maps and the tissue template created in the previous step, applying a 0.4 threshold and binarizing the tissue templates, and

finally generating the tissue masks by applying the prior in native space to the binarized tissue probability map.

Following this, for every individual subject the placement of the MRS voxel was applied as a 20x20x20 mask (individually measured for each subject based on 1H-MRS acquisition) to the three respective tissue maps providing a segmentation quantity for each tissue in the specific 1H-MRS voxel placement. CSF, GM and WM were then accounted for in the expression of Glu and GABA levels using LCModel (Gasparovic et al., 2006); corrected metabolite levels are referred to as Glu Corr and GABA Corr using the formula Glu Corr = (Glu*(43300*GMV + 35880*WMV + 55556*CSF))/(35880*(1−CSF)) and GABA Corr = (GABA*(43300*GMV + 35880*WMV + 55556*CSF))/(35880*(1−CSF)).

To test for demographic differences between LS and HS groups we used chi square or independent sample t-tests. Differences between LS and HS groups in mPFC metabolite levels, as well as SNR, Line Width and CRLB were established using multivariate analysis of variance (MANOVA) to control for multiple testing. Effects of resilience were investigated using logistic regression with resilience (CD-RISC scores) and metabolite concentrations as predictors and SPQ group (low, high) membership as the outcome. All analyses are conducted in R and reported at a significance level of $p < .05$. There were no a-priori hypotheses for other 1H-MRS metabolite levels as our focus was on GABA and Glu metabolite concentrations due to their key role in neuropathology of schizophrenia and in psychosis risk (Egerton et al., 2017; Marsman et al., 2013). For completeness, NAA, Myo-Inositol and Creatine (commonly reported metabolite concentrations) are reported in Supplementary Materials.

7.3. Results

Due to the differing sample for GABA and Glu metabolite concentrations resulting from quality control checks of the metabolite levels we report the results separately.

7.3.1. MRS GABA metabolite concentrations

Table 1 summarises the sociodemographic sample characteristics for the analysis of GABA metabolite concentrations in LS and HS groups. HS and LS groups were matched for Gender, Age and IQ but differed on all schizotypy measures, as intended by design. ANOVA revealed that HS groups had significantly lower GM, WM and CSF tissue volumes in the mPFC voxel compared to LS. Summaries of the quality check data for the GABA set by group are presented in Table 2. No significant differences between groups were detected for SN ratio, Line width or CRLB. Using corrected metabolite concentration values, ANOVA showed that the HS group ($M = 1.73$, $SD = 0.92$) had significantly lower GABA Corr levels than the LS group ($M = 2.36$, $SD = 0.62$), $F(1,38) = 6.62$, $p = 0.01$, $\eta^2 = 0.15$ (Fig 2a). A logistic regression showed that the interaction between GABA_Corr values and CD-RISC scores (resilience) was a significant fit of the model, $\chi2(3) = 43.3$, $p < 0.04$, Cox and Snell's $R^2 = 0.42$, Nagelkerke's $R^2 = 0.73$. The interaction between GABA_Corr values and CD-RISC scores was a significant predictor of SPQ group membership, $b = 0.17$ ($SE = 0.05$), $z = 3.08$, $p < 0.01$ (Fig 2). The odds of a participant with high GABA and high resilience being in the low schizotypy group are 1.18 higher than those with low GABA and low resilience (95% CI 1.07-1.34).

Table 1. Demographic summary of questionnaire and tissue maps across the HS and LS groups for GABA metabolite analysis.

Characteristic	LS (n = 21)	HS (n = 19)	F/χ2	p
Gender (male/female)	5/16	6/13	0.03	0.84
Age (years)	19.13 (SD = 2.10)	19.87(SD= 1.05)	1.05	0.31
IQ Score	93.95 (SD = 9.13)	92.89 (SD = 9.69)	0.12	0.72
SPQ Total	6.86 (SD = 3.34)	45.8 (SD = 3.39)	133.7	< 0.01
SPQ Cognitive Perceptual Factor	2.67 (SD = 2.13)	20.8 (SD = 3.96)	335.53	< 0.01
SPQ Interpersonal Factor	3.14 (SD = 2.26)	20.1 (SD = 3.81)	299.32	< 0.01
SPQ Disorganised Factor	1.67 (SD = 2.42)	10.7 (SD = 2.84)	118.86	< 0.01
Resilience	61.5 (SD = 13.7)	74.1 (SD = 13.0)	8.91	< 0.01
WM volume	0.36 (SD = 0.03)	0.27 (SD = 0.07)	27.15	<0.01
GM volume	0.42 (SD = 0.03)	0.29 (SD = 0.11)	24.17	<0.01
CSF volume	0.16 (SD = 0.02)	0.12 (SD = 0.03)	19.73	<0.01

Table 2. Summary of quality measures for the GABA dataset and Glu dataset based on group and total sample.

GABA	LS	HS	Total	Analysis (HS vs LS), F statistics
mPFC GABA	LS (n = 21)	HS (n = 19)	Total (n = 40)	
SN Ratio	53.23 (SD = 9.98)	51 (SD = 5.24)	52.23 (SD = 7.82)	0.005, p = 0.34
Line width in Hz	6.68 (SD = 1.23)	5.76 (SD = 1.85)	6.27 (SD = 1.64)	0.006, p = 0.7
GABA CRLB (in %)	14.80 (SD= 3.17)	14.17 (SD = 2.50)	14.52 (SD = 2.88)	0.05, p = 0.49
Glu				
mPFC Glu	LS (n = 26)	HS (n = 25)	Total (n = 51)	
SN Ratio	52 (SD = 9.04)	51.4 (SD = 6.64)	51.70 (SD = 7.88)	0.005, p = 0.78
Line width in Hz	6.76 (SD = 1.15)	5.97 (SD = 1.77)	6.20 (SD = 1.58)	0.006, p = 0.6
Glu CRLB (in %)	5.84 (SD= 1.97)	5.16 (SD = 1.65)	5.50 (SD = 1.83)	0.07, p = 0.18

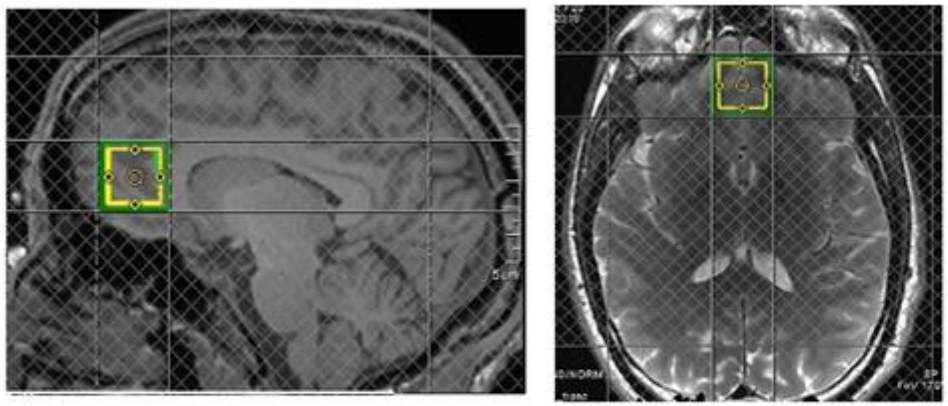


Fig 1. Voxel placement in the mPFC used in the current study.

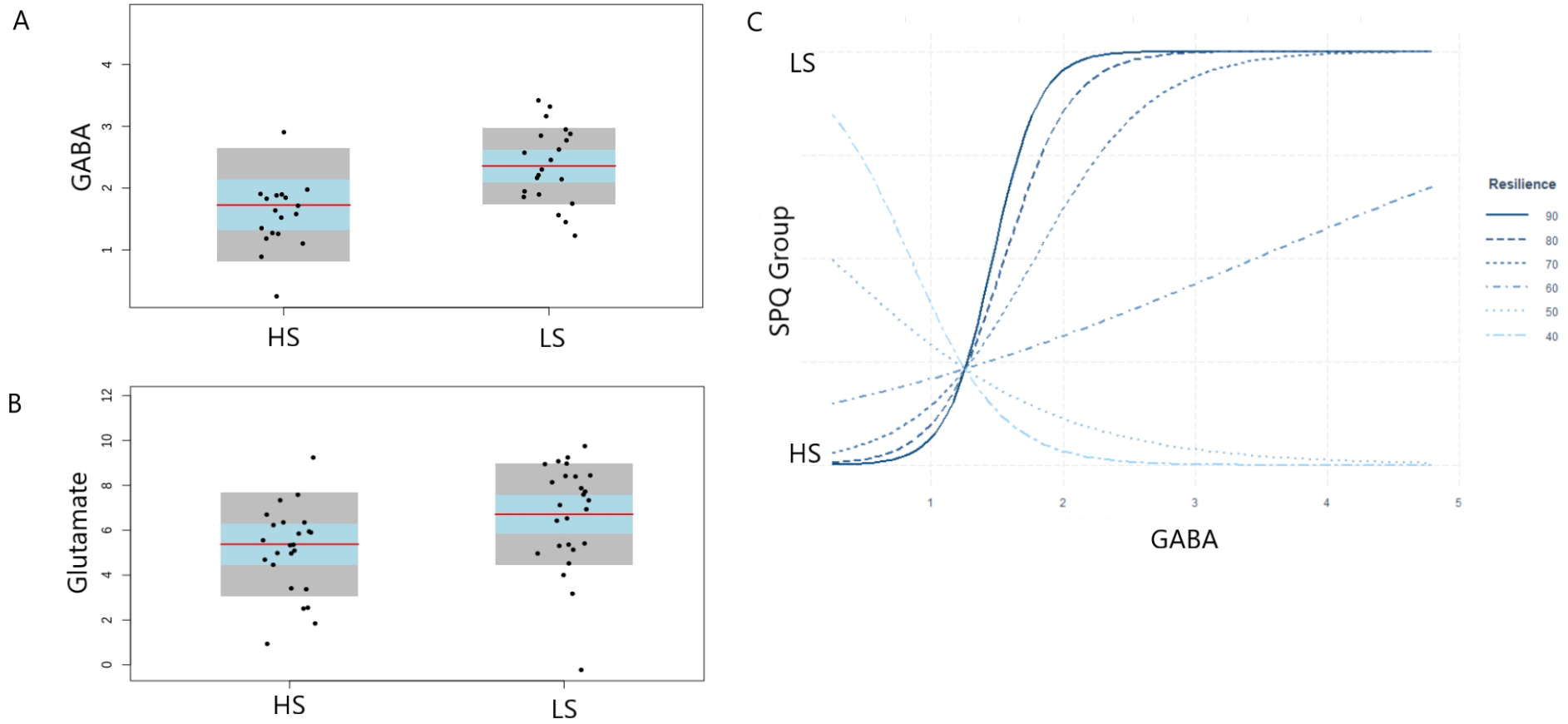


Fig 2. A) GABA corrected levels and B) Glu corrected levels by SPQ groups. Error bars show the standard error of the mean. C) Logistic regression interaction effect with GABA_Corr levels on the x axis and SPQ Group membership on the y axis, resilience is presented at the distributions of the resilience scores in the data.

7.3.2. MRS Glu metabolite concentrations

Table 3 summarises the sociodemographic sample characteristics for the analysis of Glu metabolite concentrations in LS and HS groups. HS and LS groups were matched for Gender, Age and IQ but differed on all schizotypy measures, as intended by design. Similarly, to the results from the GABA analysis, HS groups showed significantly lower GM, WM and CSF tissue volumes compared to LS. Summaries of the quality check values for the Glu set based on group are presented in Table 2. Using Glutamate corrected metabolite concentration values, ANOVA showed that the HS group (M = 5.38, SD = 2.32) had significantly lower Glu Corr levels than the LS group (M = 6.71, SD = 2.28), F (1, 49) = 4.29, p = 0.04, $\eta^2 = 0.08$ (Fig 2b). Linear regression showed no significant interaction effects between glutamate levels and CD-RISC (resilience) scores.

Table 3. Demographic summary of questionnaire and tissue maps across the HS and LS groups.

Characteristic	LS (n = 26)	HS (n = 25)	t/χ2	p
Gender (male/female)	7/19	8/17	0.05	0.93
Age (years)	19.25 (SD = 2.14)	19.94(SD= 1.35)	1.04	0.32
IQ Score	95.1 (SD = 9.16)	93.8 (SD = 9.80)	0.26	0.61
SPQ Total	7.5 (SD = 3.65)	47.2 (SD = 5.28)	980.48	< 0.01
SPQ Cognitive Perceptual Factor	2.69 (SD = 1.95)	20.7 (SD = 5.06)	284.21	< 0.01
SPQ Interpersonal Factor	3.65 (SD = 2.67)	21.3 (SD = 4.20)	324.13	< 0.01
SPQ Disorganised Factor	1.85 (SD = 2.31)	10.8 (SD = 2.69)	164.68	< 0.01
Resilience	73.58 (SD = 12.93)	58.36 (SD = 14.23)	15.93	< 0.01

WM volume	0.34 (SD = 0.07)	0.27 (SD = 0.07)	13.82	< 0.01
GM volume	0.41 (SD = 0.06)	0.29 (SD = 0.11)	20.03	< 0.01
CSF volume	0.16 (SD = 0.02)	0.12 (SD = 0.03)	20.91	< 0.01

7.4. Discussion

Using 1H-MRS, the present study found that, relative to the LS group, the HS group had significantly lower mPFC GABA and glutamate metabolites concentrations. These results are in line with previous studies in schizophrenia populations which show that patients have lower mPFC GABA levels compared to healthy controls (Marsman et al., 2013; Öngür, Prescot, McCarthy, Cohen, & Renshaw; 2010; Zhilei et al., 2015; Rowland et al., 2013). It should be noted however that other studies have reported increased mPFC GABA metabolite concentrations or no differences between patients and healthy controls (see Egerton et al., 2017 for a review). Studies investigating metabolite concentrations in individuals at high clinical risk for psychosis, similarly to schizophrenia studies, have also found increased (Tayoshi et al., 2010), decreased (de la Fuente-Sandoval et al., 2016) or no differences in GABA levels in at-risk populations relative to healthy controls (Chen et al., 2014; Da Silva et al., 2019; Menschikov et al., 2016). Findings are further complicated by reports that in clinical-high risk individuals, mPFC GABA levels are negatively correlated with the severity of negative symptoms (Menschikov et al., 2016) and that unaffected siblings have significantly lower GABA levels compared with controls (Chen et al., 2014).

Despite inconsistent findings in humans, animal models of schizophrenia indicate that dysfunction of the GABAergic neurotransmitter system plays a major role in the pathophysiology of schizophrenia (Du & Grace, 2013; Grace, 2010). The MAM model of

psychosis suggests a link between disrupted cortical GABAergic function and the dysregulation of hippocampal dopaminergic signalling (Grace, 2010). The model posits that dopaminergic hyperactivity is an indirect consequence of the reduced number of parvalbumin inhibitory interneurons in the hippocampus and the PFC (Lodge & Grace, 2008; Zhang, Sun & Reynolds, 2002). Parvalbumin interneurons contain and release GABA that inhibits, or limits, the activity of the neurons that provide output from the hippocampus and prefrontal cortex (Grace, 2010). Indeed, studies revealed that MAM rats show a selective loss of parvalbumin-containing interneurons in both the hippocampus and the prefrontal cortex (Lodge, Behrens & Grace, 2009). The mPFC can regulate hippocampal and subcortical dopamine neuron activity via the nucleus reuniens of the thalamus (Grace, 2010). Thus, the current finding of reduced mPFC GABA levels in high schizotypy participants is broadly consistent with diminished GABAergic regulation from the mPFC shown in the MAM model of psychosis, but whether this is due to a reduced density of parvalbumin interneurons (as shown in the animal model) cannot be established using MRS.

Further, we found a significant interaction between resilience scores (the ability to cope with stress and trauma) and mPFC GABA metabolite concentrations predicted schizotypy group (low, high). This result may provide support for the well-established role of stress in the development of psychosis as the analyses shows that participant with high mPFC GABA levels and high resilience to stress are significantly more likely to be in the low SPQ group than participants with lower GABA resilience levels. Whilst it is difficult to interpret this finding, it is possible that higher prefrontal GABA metabolite concentration and high resilience to stress are factors that confer a lower risk of psychosis proneness.

Cortical glutamate levels were also found to be significantly lower in high compared to low schizotypy individuals, a finding consistent with some previous studies in patients with

schizophrenia (Marsman et al., 2013; Öngür et al., 2010; Goto et al., 2009). However, as with studies of GABA metabolite concentrations, increased cortical glutamate has also been reported in patients with schizophrenia (Choe et al., 1996; Rüsch et al., 2008; Moore, Jentsch, Ghajarnia, & Geyer; 2006). Mixed results are also reported in studies investigating clinical high-risk samples, where decreased (Natsubori et al., 2014) and increased cortical glutamate levels have been reported (Stone et al., 2009). Animal models of psychosis generally posit a role for increased glutamate levels, particularly in medial temporal lobe regions, that leads to reduced hippocampal volume (Lieberman et al., 2018) and increased subiculum output to the ventral striatum via glutamatergic pathways (Moore et al., 2006; Lodge and Grace, 2011). However, decreased glutamate levels have been reported in the mPFC in MRS studies of patients with schizophrenia and CHR samples (Marsman et al., 2013), consistent with the current findings in high schizotypy individuals. The glutamatergic system is believed to affect synaptic plasticity and cortical microcircuitry, in particular NMDA-receptor signalling (Harrison & Weinberger, 2005). NMDA-receptor antagonists, such as ketamine and phencyclidine (PCP) which reduce glutamatergic signalling, induce symptoms that mimic the positive and negative symptoms seen in schizophrenia (Adams & Moghaddam, 1998; Krystal, et al., 1994; Moghaddam et al., 1997). Injection of these NMDA-receptor antagonists leads to decreased glutamate levels (Marsman et al., 2013; Moghaddam et al., 1997; Rowland et al., 2005) and animal studies show that the absence of NMDA-receptor subunits can cause alterations at the molecular and behavioural level and produce schizophrenia-like symptoms (Marsman et al., 2013).

Changes in cortical inhibitory and excitatory signalling may result in a loss of synchronous cortical activity (Lisman et al., 2008; Lewis, Curley, Glausier & Volk, 2012) and underlie the behavioural deficits commonly reported in schizophrenia and psychosis risk populations (Lisman et al., 2008; Lewis et al., 2012), such as emotional processing (Keefe,

Eesley & Poe, 2005) and social cognition (Kozhuharova, Saviola, Ettinger & Allen, 2020). A recent systematic review conducted by our research group reported that both high schizotypy and clinical at-risk populations present with a tendency towards increased activity in frontal cortex during various emotional and social cognition tasks (Kozhuharova et al., 2020). Thus, the reduced mPFC GABA concentrations observed in the current study may underlie some of the cognitive, affective and social cognition deficits reported in psychosis risk populations. Although much more work is needed to investigate the relationship between cortical GABA/glutamate signalling and behavioural measures, one previous study investigating glutamate levels in individuals with high positive schizotypy, reports that glutamate levels were negatively associated with the degree of activation to emotional pictures in the striatum and the mPFC (Modinos et al., 2017). Although we acquired no behavioural measures here, future work should examine the relationship between GABA/Glutamate and cognitive function, affective processing and emotion regulation in high schizotypy samples.

A limitation of 1H-MRS is that it measures total GABA concentrations within a relatively large voxel, which is determined a priori, and cannot discriminate between GABA levels in different cell types. This limits the application of 1H-MRS in addressing the cell- and network- specific GABA abnormalities hypothesized to occur in schizophrenia and psychosis risk (Lewis et al., 2012). For this reason, the current findings cannot inform on the specific mechanisms that might lead to reduced GABA and glutamate levels and we cannot test whether these results are due to reduced GAD67 or reduced density of parvalbumin interneurons, as suggested by animal models. The 1H-MRS GABA signal may reflect the entire GABA content of the voxel (that is, intracellular and extracellular, and involved in metabolism or neurotransmission). Recent work argues that the 1H-MRS GABA signal predominantly relates to extracellular, extra-synaptic GABA providing tonic inhibitory tone, rather than GABA involved in phasic synaptic neurotransmission (Stagg, 2014). Theoretically, the 1H-MRS

GABA signal should therefore be sensitive to GAD67 reduction, but we could not test this in the current study. Pharmacologically induced alterations in synaptic GABA may be more sensitively imaged with positron emission tomography (PET, Egerton et al., 2017). In the future, combination of this approach with 1H-MRS in the same subjects, and potentially during the same scanning session on combined PET-magnetic resonance platforms, might investigate dysfunction of synaptic versus nonsynaptic GABA and glutamate in schizophrenia.

In conclusion, the current study utilised MRS methods to investigate GABA and glutamate levels in individuals with high and low schizotypy scores. In line with predictions from animal and post-mortem studies of schizophrenia, the current study found reduced levels of both GABA and glutamate in high schizotypy individuals compared to low schizotypy. Furthermore, the interaction between GABA metabolite concentrations and resilience levels was associated with reduced schizotypy levels. The findings suggest that individuals with risk for psychosis as defined by high schizotypy scores already present with abnormal GABA and glutamate levels, which may relate to the observed deficits in cognition and perception in schizophrenia-spectrum conditions.

Supplementary Material

We report analyses for three additional commonly used metabolites, namely Creatine (CR), Myo-inositol and N-acetylaspartate (NAA). CSF, GM and WM were then accounted for in the expression of these metabolite levels using LCModel [65]; corrected metabolite levels have the affix Corr. These three metabolites were corrected using the following formula Corr = (metabolite *(43300*GMV + 35880*WMV + 55556*CSF))/(35880*(1−CSF)) (Morgenroth et al., 2019).

Differences between LS and HS groups in mPFC metabolite levels, as well as SNR, Line Width and CRLB were established using multivariate analysis of variance (MANOVA) to control for multiple testing. Summaries of the quality check data for these metabolites are presented in Table S1. The final samples included in these analyses varied following exclusion of participants due to quality control checks. For Cr, quality control checks indicated that 1 subject from the HS group had to be excluded due to CLRB ratios for Glu > 20%, resulting in a total sample of 26 HS and 26 LS individuals. For the analysis of Myo-inositol, 6 participants from the LS group and 2 participants from the HS group had to be excluded due to CLRB rations > 20%, resulting in a total sample of 20 LS and 25 HS subjects. There were no excluded participants for the NAA analysis, resulting in a total sample of 26 LS an 27 HS subjects. No significant differences between groups were detected for SN ratio, Line width or CRLB for any of these metabolites.

ANOVA showed that the HS group (M = 3.27, SD = 3.03) had significantly lower CR Corr levels than the LS group (M = 5.2, SD = 1.78), F (1,50) = -4.43, p = 0.01, $\eta 2$= 0.7. For Myo-inositol, the HS group (M = 2.37, SD = 3.33) did not differ from the LS group (M = 3.11, SD = 5.21), F (1, 43) = -1.29, p = 0.2. For NAA, the HS group (M = 4.16, SD = 6.27) had

significantly lower NAA Corr levels than the LS group (M = 7.06, SD = 3.28), F (1, 51) = -4.73, p = 0.01, η2= 0.6.

Table S1. Summary of quality measures for the Cr, Myo-inositol and NAA dataset based on group and total sample.

Cr	**LS**	**HS**	**Total**	**Analysis (HS vs LS), F statistics**
mPFC Cr	LS (n = 26)	HS (n = 26)	Total (n = 52)	
SN Ratio	53.2 (SD = 9.91)	51 (SD = 5.27)	51.8 (SD = 7.80)	0.005, p = 0.61
Line width in Hz	6.68 (SD = 1.03)	5.96 (SD = 1.45)	6.25 (SD = 1.64)	0.006, p = 0.7
Cr CRLB (in %)	3.56 (SD = 1.08)	3.72 (SD = 1.34)	3.64 (SD = 1.21)	0.8, p = 0.4
Myo-inositol				
mPFC Myo-inositol	LS (n = 20)	HS (n = 25)	Total (n = 45)	
SN Ratio	50.2 (SD = 9.32)	51.4 (SD = 6.50)	51.8 (SD = 7.62)	0.005, p = 0.64
Line width in Hz	6.76 (SD = 1.15)	5.97 (SD = 1.77)	6.38 (SD = 1.38)	0.006, p = 0.6
Myo-inositol CRLB (in %)	8.61 (SD = 5.14)	9.59 (SD = 5.46)	9.15 (SD = 5.28)	0.7, p = 0.5
NAA				
mPFC NAA	LS (n = 26)	HS (n = 27)	Total (n = 53)	

SN Ratio	53.1 (SD = 7.2)	52.4 (SD = 5.4)	52.7 (SD = 7.82)	0.005, p = 0.4
Line width in Hz	6.68 (SD = 1.34)	5.86 (SD = 1.62)	6.27 (SD = 1.34)	0.006, p = 0.7
NAA CRLB (in %)	3.84 (SD = 1.40)	4.76 (SD = 2.65)	4.31 (SD = 2.17)	-1.41, p = 0.2

Reference:

Morgenroth E, Orlov N, Lythgoe DJ, Stone JM, Barker H, Munro J, Eysenck M & Allen P. Altered relationship between prefrontal glutamate and activation during cognitive control in people with high trait anxiety. Cortex 2019; 117:53-63.

Chapter Eight

General Discussion

8.1. Social cognition, findings and conclusions

The application of functional magnetic resonance imaging (fMRI) in this thesis aimed to investigate the neural mechanisms of potentially abnormal social cognition in high vs low schizotypy individuals. Social cognition is of key significance in schizophrenia-spectrum conditions, as poor social functioning is linked to lower quality of life (Penn, Corrigan, Bentall, Racenstein, & Newman, 1997) and predicts illness outcome in schizophrenia, including relapse, poor illness course and unemployment (Álvarez-Jiménez et al., 2012; Brune, Schaub, Juckel, & Langdon, 2011; Couture, Penn, & Roberts, 2006; Kring & Elis, 2013). Studies have further shown that in schizophrenia patients, social cognitive impairments have a stronger negative effect on daily functioning than non-social cognitive impairments do (Fett et al., 2011; Green, Hellemann, Horan, Lee, & Wynn, 2012). Studies have reported that higher schizotypal traits are associated with a number of neural abnormalities during social cognition tasks (see Kozhuharova, Saviola, Ettinger, & Allen, 2020) for a review of existing studies), mainly increased activity in frontal cortex regions. The interpretation of these abnormal neural results is complicated by the lack of behavioural differences between high vs low schizotypy samples, as well by the limited knowledge of specific mechanisms driving learning from socially salient cues in these samples. To this end, we employed two separate fMRI tasks to investigate the mechanisms that could influence learning from social information in schizotypy. The first task investigated the neural correlates of socially salient (vs non-social) prediction errors in this at-

risk population during belief updating. The second task employed computational modelling to investigate hierarchical learning under uncertainty in a social probabilistic learning task.

The belief updating experimental paradigm we used here investigated updating of social and non-social information based on its valence (whether participants receive good news or bad news, (Kuzmanovic, Jefferson, & Vogeley, 2015; Kuzmanovic, Jefferson, & Vogeley, 2016; Sharot, Korn, & Dolan, 2011; Sharot & Garrett, 2016). Of particular interest was the investigation of neural correlates of negative/positive social prediction errors in high vs low schizotypy samples. As hypothesised, group analyses indicated that high schizotypy (HS) participants showed abnormal activity in prefrontal regions during social belief updating. Specifically, in HS individuals, compared to LS individuals, we observed increased activity in the ventromedial prefrontal cortex (vmPFC) and the left inferior frontal gyrus (IFG), and lower activity in the dorsolateral prefrontal cortex (dlPFC) in response to social positive and negative prediction errors. In comparison, we found no areas of hyperactivation in HS subjects in non-social interaction conditions relative to LS subjects. Overall, the current findings indicate that HS participants show increased PFC response specific to socially salient prediction errors. The findings also fit in with a number of previous schizotypy investigations that have reported increased prefrontal cortex activity during tasks of emotional processing or theory of mind (ToM; Modinos, Ormel, & Aleman, 2010; Modinos, Renken, Ormel, & Aleman, 2011; Mohanty et al., 2005; see Kozhuharova et al., 2020 for a review).

The right vmPFC is a key region responsible for social conduct, decision-making and emotional processing (Tranel, Bechara, & Denburg, 2002) and meta-analyses of fMRI data further indicate a critical role of the vmPFC in ToM ability (Molenberghs, Johnson, Henry, & Mattingley, 2016; Schurz, Radua, Aichhorn, Richlan, & Perner, 2014). A main aspect of social cognitive function putatively subserved by the vmPFC is the processing of self-relevant

information (Northoff et al., 2006; Svoboda, McKinnon, & Levine, 2006). Self-referential processing is important for social cognitive functioning, as interacting with others requires reflection on our own feelings and knowledge (Mitchell, Banaji, & MacRae, 2005; Vogeley & Fink, 2003). In the context of the belief updating task used here, vmPFC activity could reflect self-referential processes as the task requires participants to consider the average base rates of events in the context of judging the likelihood of these events happening to them in the future. We speculate that the higher vmPFC activity in HS subjects could suggest that the prefrontal cortex in these individuals is particularly sensitive to self- and other- referential processing and has to exert higher levels of activity to achieve a behavioural performance similar to that of controls (as in the current study, there were no behavioural differences between HS and LS subjects). This interpretation fits in with clinical cases, where research consistently finds that schizophrenia is associated with functional and behavioural deficits during various social cognitive and self-referential tasks activating the vmPFC (Ditman & Kuperberg, 2005; Fisher, McCoy, Poole, & Vinogradov, 2008; Honea, Crow, Passingham, & Mackay, 2005; Hooker, Bruce, Lincoln, Fisher, & Vinogradov, 2011; Park, Park, Chun, Kim, & Kim, 2008; Parnas & Sass, 2001; Pomarol-Clotet et al., 2010; Seal, Aleman, & McGuire, 2004; Williams et al., 2008).

A complementary explanation is that the higher prefrontal cortex activity in HS subjects in response to social (both positive and negative) prediction errors in the context of comparable behavioural performance suggests there is abnormal processing of these learning signals in HS subjects. The vmPFC is indeed a key region involved in value-based decision-making across various paradigms (Bechara, Tranel, & Damasio, 2000; Camille, Griffiths, Vo, Fellows, & Kable, 2011; Fellows & Farah, 2003; Henri-Bhargava, Simioni, & Fellows, 2012; Krajbich, Adolphs, Tranel, Denburg, & Camerer, 2009; Pujara, Wolf, Baskaya, & Koenigs, 2015; Wheeler & Fellows, 2008). Similarly, functional imaging studies have linked vmPFC activity

with the representation of value and reward processing in a variety of decision-making contexts (Levy & Glimcher, 2012; Liu, Hairston, Schrier, & Fan, 2011). The reward processing and decision-making functions of vmPFC are thought to depend, in part, on interactions with the ventral striatum and amygdala. The vmPFC and the ventral striatum are often co-activated during reward processing tasks (Cauda et al., 2011) and animal research even suggests a causal effect of vmPFC activity on ventral striatum activity. Rodent studies have shown that vmPFC has direct glutamatergic projections to the ventral striatum (Gabbott, Warner, Jays, Salway, & Busby, 2005; Sesack, Deutch, Roth, & Bunney, 1989; Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004) and that inactivation of vmPFC alters neuronal activity in ventral striatum (Ghazizadeh, Ambroggi, Odean, & Fields, 2012). Lesioning or inactivating both vmPFC and ventral striatum/accumbens disrupts behavioural responding during reward learning and reaction time tasks, indicating that adaptive decision-making depends on concurrent activation of both regions (Bossert et al., 2012; Christakou, Robbins, & Everitt, 2004; Feja & Koch, 2015; Onge, Stopper, Zahm, & Floresco, 2012; Peters, LaLumiere, & Kalivas, 2008; Richard & Berridge, 2013; Smith & Graybiel, 2013). Here, we found increased vmPFC activity in trials tracking both positive and negative prediction errors for social updating, but there were no activation differences between HS and LS subjects in the striatum. Given the causal effect of vmPFC activity on striatum, an explanation for the current results could be that in HS individuals, hyperactivity of the PFC regions is required in order to project enough concurrent activation to midbrain regions such as the striatum and ensure similar behavioural performance in response to prediction errors. We offer a similar explanation for the higher activity in the left IFG in HS subjects in response to estimation errors for social events. The IFG is involved in error-monitoring and reversal learning (Cools, Clark, Owen, & Robbins, 2002), risk prediction error (d'Acremont, Lu, Li, Van der Linden, & Bechara, 2009) and it tracks and integrates information into prior beliefs (Garrett et al., 2014; Sharot et al.,

2011). The greater IFG activity in response to socially salient estimation errors might reflect a higher effort to integrate social information into prior beliefs and a need for an overweighted prefrontal cortex response to prediction errors in order to achieve normal behavioural performance.

In addition, we found greater dlPFC activity in LS subjects compared to HS subjects in response to social positive estimation errors. This region has primarily been associated with its role in executive functions (Mansouri, Tanaka, & Buckley, 2009) partly by providing a representation of context cues such as relevant environmental rules or stimulus-response mappings (Barch et al., 1997; Cohen et al., 1994; Delawalla, Csernansky, & Barch, 2008; MacDonald III & Carter, 2003; Sylvester et al., 2003). The dlPFC also represents currently experienced, incompatible or conflicting stimuli or rules or their associated responses; i.e. the region encodes a neural representation of conflict as a distinct task-relevant variable; maintains conflict information within and across trials; and implements executive control (Mansouri et al., 2009). The findings of higher activity in this region in LS subjects, in comparison to HS subjects, in response to social positive errors might suggest that executive and inhibitory control is impaired in HS individuals and might suggest a problematic contextual integration of social information with good/positive feedback. This interpretation would be in line with findings that schizophrenia patients are impaired in contextual processing as characterised by lower dlPFC activity (Barch et al., 2001; Delawalla et al., 2008; Holmes et al., 2005; MacDonald III & Carter, 2003).

Overall, the current findings from the belief updating task strongly support the notion that HS subjects present with abnormal processing of positive and negative prediction errors that moderate belief updating, specifically in a social context compared to non-social belief updating. These findings can explain the higher prefrontal cortex activity observed in HS

samples across a variety of social cognition studies (combined with lack of behavioural differences as observed here; Kozhuharova et al., 2020), as prediction errors drive learning in any cognitive paradigm; (Iglesias et al., 2013; Pessiglione, Seymour, Flandin, Dolan, & Frith, 2006; Steinberg et al., 2013; Tobler, O'Doherty, Dolan, & Schultz, 2006).

The prefrontal cortex in these samples presents with an abnormal neural response to errors in particular in social tasks, and thus may have to exert higher activation to allow these informative predictive errors to drive belief updating in order to maintain task performance. Studies have also found aberrant activity in prefrontal cortex (and ventral striatum) in people with schizophrenia during expected and unexpected outcomes (Gradin et al., 2011; Koch et al., 2010; Krawitz, Braver, Barch, & Brown, 2011; Morris et al., 2012; Murray et al., 2008; Walter, Kammerer, Frasch, Spitzer, & Abler, 2009; Waltz et al., 2009). Our findings are also in line with a previous study reporting that schizotypy traits are significantly correlated with aberrant frontal and striatal prediction error signal during non-social learning (Corlett & Fletcher, 2012). These findings also provide support for a hierarchical processing model where schizophrenia symptoms, particularly delusions, arise from aberrations in how the brain circuits specify hierarchical predictions and how they compute and respond to prediction errors (Corlett, Taylor, Wang, Fletcher, & Krystal, 2010; Fletcher & Frith, 2009). This idea of a hierarchically organized system draws on the predictive coding theory of cortical function in which a primary purpose of cortical interactions is to minimize prediction error in pursuit of maximizing the accuracy of predictions about states in the environment and thus optimizing behaviour (Friston, 2005).

Since prediction error is the driving force in shaping such a system and since the HS subjects in the current cohort are characterised by functional abnormalities in neural activity in response to prediction errors, we argue that the neural signature of schizotypal traits overlaps

with prediction error dysfunction observed in psychosis (Corlett et al., 2007; Corlett et al., 2006; Murray et al., 2008). However, while in clinical presentation these neural abnormalities lead to aberrant behavioural performance (Corlett, Honey, & Fletcher, 2007; Corlett et al., 2007; Ermakova et al., 2018; Kapur, 2003; Morris et al., 2012; Murray et al., 2008), in HS subjects these neural abnormalities present as compensatory mechanism exerting higher activity in response to prediction errors in order to allow individuals at the lowest risk for psychosis to function at the same level as controls.

In order to further gain understanding of the processing of prediction errors in schizotypy samples and how these neural abnormalities reflect schizotypy behaviour, we employed a social probabilistic learning task using a combination of fMRI and computational models. The computational models employed here, namely hierarchical Bayesian models, view perception and learning as a hierarchically organised process, in which beliefs at multiple levels, from concrete (e.g., specific stimuli) to more abstract aspects of the environment (e.g., probabilities and volatility), are updated based on level-specific prediction errors (PEs) and precisions. Specifically, under fairly general assumptions (i.e., for all probability distributions from the exponential family) a ratio of precisions (of bottom-up input vs. prior beliefs) serves to scale the amplitude of PE signals and thus their impact on belief updates (Mathys, Daunizeau, Friston, & Stephan, 2011; Mathys et al., 2014). The central idea here is that the brain instantiates a generative model of its sensory inputs, i.e. a model that makes predictions about the environment and how its (hidden) state gives rise to sensations (Mathys et al., 2011; Mathys et al., 2014). Perceptual inference rests on inverting the model to determine the most likely cause of sensory input; learning serves to update beliefs such that future sensory inputs can be better predicted. Importantly, under very general assumptions, these belief updates have a generic form: they are proportional to prediction errors, weighted by a precision ratio that serves as a dynamic learning rate and balances the expected precision of low-level (e.g.,

sensory) input against the precision of prior beliefs (Mathys et al., 2014). The corollary from this general update rule is that unusually pronounced belief updates can arise from two sources: by assigning too much precision to sensory inputs, or by overly uncertain prior beliefs. Here, we employed this Bayesian framework to test learning under uncertainty in a probabilistic task that involved participants learning simultaneously from social cues (i.e. advice given from another person) and non-social cues (i.e. probabilities of a certain colour card winning). The application of this model allowed us to gain a precise understanding of the impairments that HS subjects have during learning.

First, we found no group differences for the social bias response model parameter in the model, suggesting that both LS and HS participants put equal weight on the learned social prediction relative to the learned non-social prediction when making decisions. Thus, our results submit that social biases are not simply a resistance to accepting advice (i.e. social feedback) from others but are consistent with abnormal hierarchical learning.

We further found specific behavioural differences between HS and LS subjects that were specific to HS as a sample, not a specific subfactor. The HS individuals presented with higher initial prior for volatility (i.e. changes in environment) suggesting that they expected the advice to be more volatile. They also presented with higher expected uncertainty about stimulus-outcome relationships, i.e. they changed beliefs excessively about stimulus-outcome associations in the task more quickly. Compared to LS, HS individuals had faster learning at the lower level (learning about stimulus-outcome) associations, but these beliefs were not influencing learning about the volatility of the environment/task. In other words, HS subjects' expectations about advice volatility are quicker to update in response to unexpected uncertainty in associations, yet they present with greater reliance on higher-level priors than on task feedback. By relying more on their expectations of volatility than their actual experience, HS

subjects are also slower to learn about changes in task volatility as manifested by decreased meta-volatility learning rates. HS individuals were selectively impaired by stable vs volatile task phases and presented with larger estimates about the environmental volatility during volatile phases, i.e. they believed the environment to be more volatile than it actually was. HS participants also presented with a higher third-level, volatility precision-weighted PEs (the prediction error that drives learning about global changes in the environment) for both stable and volatile conditions indicating that – irrespective of the phase of the task - they perceive the environment as more volatile than predicted, regardless of actual task phase/feedback. Thus, our results suggest that HS subjects present with abnormal learning under uncertainty and they overestimate the volatility of social advice. They rely more on their prior beliefs and are reluctant to update these beliefs in response to feedback.

In line with previous work in hierarchical learning under volatility in CHR individuals (Cole et al., 2020) and schizophrenia patients (Adams, Stephan, Brown, Frith, & Friston, 2013; Powers, Mathys, & Corlett, 2017; Woodward, Moritz, Cuttler, & Whitman, 2006), our findings in high schizotypy subjects suggest that the earliest risk cohort for psychosis already presents with an abnormal mechanism for processing volatility (according to the behavioural data) which is observed during social learning. This higher average level of estimated volatility over time signifies an increase in uncertainty in advice-outcome associations, represented by strong higher beliefs about volatility and reduced learning rates at that level. This strong belief in the volatility of social information necessitates hypervigilance and potentially makes it difficult to change social associations. If HS individuals rely mainly on higher volatility priors of social information and adhere to expectations over evidence, this could be a potential mechanism explaining the difficulties in social functioning observed in these populations (Miller & Lenzenweger, 2012). Recent work has reported that, similarly to schizophrenia patients, high schizotypy individuals have impairments in friendship relations, family relations

and interpersonal engagement even when cognitive and emotional skills are unaffected (Aghvinian & Sergi, 2018). Our results would suggest that the learning mechanisms that drive these relationships are impaired in HS individuals, leading to abnormal hypervigilance as driven by the expectation of over-volatility. Similarly, the results could explain the aberrant salience deficits and jumping to conclusion biases observed in schizotypy samples (Chun, Gross, Mielock, & Kwapil, 2020; Chun, Kwapil, & Brugger, 2019; Cicero, Becker, Martin, Docherty, & Kerns, 2013; Cole et al., 2020; Haselgrove et al., 2016; Juarez-Ramos et al., 2014; O'Tuathaigh et al., 2020; Sellen, Oaksford, & Gray, 2005). Similar computational models have been used to explain aberrant salience in schizophrenia patients as well, where high-order beliefs of abnormally low precision (Adams et al., 2013) render the environment seemingly unpredictable (e.g. more volatile).

The neural pattern of activation in response to these computational parameters further suggests abnormally attenuated processing of PEs, thus supporting the notion of abnormal hierarchical learning in HS samples. As in previous work, we found that prior beliefs about volatility activates a network of regions across the cerebellum, cuneus, temporal gyri and parahippocampal gyri (Cole et al., 2020; Powers et al., 2017). Group contrasts showed that activations in these areas are higher in LS subjects compared to HS subjects, while HS subjects showed higher activity across the superior frontal gyrus. While the behavioural results indicate that HS subjects present with higher estimated volatility during volatile task phases, they also presented with lower meta-volatility across the whole task. Thus, these relative deactivations in key neural regions in HS subjects during decision-making suggests there is an atypical cortical representation of environmental volatility in these samples.

Furthermore, our investigations of lower-level precision-weighted PEs across the sample report results similar to previous work, with key activated regions including midbrain,

cerebellum, middle frontal gyrus, middle temporal gyrus, anterior cingulate cortex and insula (and activations in midbrain in response to outcome-related precision-weighted prediction errors; (Cole et al., 2020; Diaconescu et al., 2017; Iglesias et al., 2013). Importantly, in the current study, the neural investigations of group comparisons show that HS subjects present with attenuated neural processing of both level precision-weighted PEs, i.e. prediction errors about the stimulus-outcome associations and about the volatility of the environment. LS subjects showed higher activity in the midbrain, insula, middle and superior temporal gyri in response to low-level (outcome) precision-weighted PEs, while HS subjects showed higher activity in the anterior cingulate cortex and the middle frontal gyrus. One mechanistic explanation for the observed underweighting (in terms of neural encoding) of low-level PEs could be an increased precision of higher-level beliefs in HS individuals; in other words, HS may be characterised by abnormal estimates of environmental uncertainty as observed across the behavioural data. Similar results were observed for high-level PEs, where LS subjects presented with higher activity in the cholinergic brainstem, insula, paracingulate gyrus and middle/superior temporal gyrus and HS subjects presented with higher activity in the middle frontal gyrus. HS subjects, on the other hand, presented with reduced expression of high-level volatility precision-weighted PEs relative to LS subjects, suggesting that they inform updates about volatility less.

Group comparisons across all computational parameters of interest returned an increased activity in frontal regions in HS subjects compared to LS subjects, including the middle frontal gyrus and parts of the anterior cingulate cortex. Activations of the prefrontal cortex have been reported when participants simulated others' intentions (Behrens, Hunt, Woolrich, & Rushworth, 2008; Frith & Frith, 2006; Frith & Frith, 2012) and decisions (Nicolle et al., 2012) and are commonly associated with a broad network responsive for mentalizing and ToM cognition (Ochsner, 2008; Phan, Wager, Taylor, & Liberzon, 2002). The current

findings of increased frontal activity in response to social learning in HS subjects across a variety of socially relevant computational parameters are in line with the majority of previous work in social cognition in schizotypy samples and with our findings in the belief updating task (see Kozhuharova et al., 2020 for a review). The consistent patterns of increased activity in PFC regions in HS samples during a social cognition task further supports the notion that the HS state is characterised by abnormal processing of socially salient cues leading to aberrant beliefs about others' intentions and thus contributing to the formation of delusions (Corlett et al., 2010; Morrison, Renton, Dunn, Williams, & Bentall, 2004). In line with this finding, we observed a higher neural activity in HS samples in response to the environmental uncertainty of the advice. HS subjects presented with increased activity in the superior/inferior frontal gyri, indicating that they overweight the environmental uncertainty of the social information.

These findings are of key importance for social cognition and beyond. Taken together, the results suggest that HS subjects present with abnormal processing of prediction errors and have to exert higher prefrontal cortex control to reach a behavioural performance similar to LS subjects. By using more precise analytical approaches, namely computational models, we identified that a key cause for this abnormal learning is the overestimation of volatility in these samples and the aberrant learning about global feedback. Combined with the neural underweighting of PEs in these samples, the findings suggest that prediction errors both about immediate stimulus-outcome associations and about global environment in HS samples are abnormal and lead to aberrant learning about the environment. The current findings refer to social cognition, but the learning mechanisms identified here may be similar to other forms of hierarchical learning outside of a social context, consistent with models that have been used to explain other cognitive deficits in schizophrenia such as aberrant salience (Adams et al., 2013). We speculate that the higher prefrontal activity observed across the two tasks represents a compensatory mechanism that allows HS subjects to perform in daily functions on a level,

similar to controls. Yet, even at the earliest risk stage HS subjects already present with underweighting of PEs in key neural regions and with abnormally high volatility priors, suggesting that these particular learning components can be involved in progression to psychosis and their further impairment might lead to clinical presentation.

This assumption is supported by the putative relation of outcome-related PEs to phasic dopamine release and possible involvement in dysfunctional learning in psychosis and schizophrenia (Adams et al., 2013; Corlett et al., 2007; Corlett et al., 2010; Corlett, Frith, & Fletcher, 2009; Ermakova et al., 2018; Gradin et al., 2011; Murray et al., 2008; Pessiglione et al., 2006; Schultz, Dayan, & Montague, 1997). Specifically, schizophrenia involves increased dopamine synthesis in the striatum (Fusar-Poli & Meyer-Lindenberg, 2013; Weinberger & Laruelle, 2001), even in medication-naive prodromal patients (Howes et al., 2009). Furthermore, patients at ultra-high risk of psychosis who later transition to psychosis have greater dopamine synthesis than those who do not (Howes et al., 2011) and show an increase in dopamine synthesis from the prodromal stage to psychosis (Howes et al., 2011). The dopaminergic PE signal is thought to represent a neural response to deviation from an expected outcome (Gardner, Schoenbaum, & Gershman, 2018; Iglesias et al., 2013; Suarez, Howard, Schoenbaum, & Kahnt, 2019) and likely supports the updating of beliefs about the environment by induction of synaptic plasticity (Montague, Hyman, & Cohen, 2004). In humans, this has been supported by fMRI studies that have demonstrated the presence of reward PE signals in the dopaminergic midbrain (e.g. (D'Ardenne, McClure, Nystrom, & Cohen, 2008; Diuk, Tsai, Wallis, Botvinick, & Niv, 2013; Klein-Flügge, Hunt, Bach, Dolan, & Behrens, 2011) or in regions targeted by its projections, such as the striatum (Gläscher, Daw, Dayan, & O'Doherty, 2010; McClure, Berns, & Montague, 2003; Murray et al., 2008; O'Doherty, Dayan, Friston, Critchley, & Dolan, 2003; Pessiglione et al., 2006; Schonberg et al., 2010). Furthermore, reward- and prediction error-related behaviours are sensitive to dopaminergic perturbations. A

drug that upregulated dopamine function in healthy participants strengthened error-dependent reward learning, whereas a dopamine-blocking drug reduced such learning (Pessiglione et al., 2006). The dopamine system is a key area implicated in the progression to psychosis and is abnormal in both clinical-high risk and schizophrenia patients (Allen et al., 2019; Gomes & Grace, 2017; Howes et al., 2012; Howes, & Nour, 2016; Kapur, 2003; Lodge & Grace, 2011; Winton-Brown, Toby T., Fusar-Poli, Ungless, & Howes, 2014). Findings in schizotypy samples suggest that HS may benefit from dopamine agonists in terms of cognitive performance, while LS subjects may deteriorate in cognition with these agonists (Mohr & Ettinger, 2014). Thus, data suggests that dopamine impacts some of the cognitive deficits observed in high schizotypy (Giakoumaki, 2012; Mohr, Landis, Bracha, Fathi, & Brugger, 2005). There is also evidence of increased striatal dopamine release following amphetamine administration or stress induction in schizotypy (Abi-Dargham et al., 2004; Soliman et al., 2008). Thus, there is preliminary evidence to suggest that variance in schizotypy traits may be linked to alterations of the dopamine system. The current findings would fit with this line of work, as the dopaminergic midbrain showed deactivation in HS subjects in response to PEs.

Finally, the findings indicate that these neural abnormalities in response to PEs are characteristic of total high schizotypy, not just high positive schizotypy. Indeed, dopamine abnormalities leading to abnormal learning can be used to explain both positive symptoms (delusions, hallucinations) and negative symptoms (avolition, social withdrawal, apathy). Under normal circumstances, it is the context driven activity of the dopamine system that mediates the experience of novelty and the acquisition of appropriate motivational salience (Berridge & Robinson, 1998; Berridge, 2007; Berridge, 2012; Heinz, 1999; Kapur, Mizrahi, & Li, 2005) and the abnormal dopamine system in schizophrenia results in a system which fires and releases dopamine independent of cues and context (Kapur, 2003). The aberrant salience resulting from this abnormal activity means that patients experience an increasing sense of

perplexity, confusion and alterations in behaviour which crystalize in a delusion(Kapur, 2003; Kapur et al., 2005). Positive symptoms in this framework are a top-down cognitive explanation that the individual imposes upon these aberrant salience experience in an effort to make sense of them (Kapur, 2003). Indeed, pharmacological studies confirm that dopamine affects both performance and learning (Beeler et al., 2012; Cagniard et al., 2006; Collins & Frank, 2014; Wise, 2004). Similarly, impairments in the direct pathway of dopamine receptors (via striatal neurons which facilitates the most appropriate actions) correlates with negative symptoms as well (Gold et al., 2012; Strauss et al., 2011; Yılmaz, Simsek, & Gonul, 2012). Similarly, medicated patients show blunted neural responses for positive PEs in the striatum, midbrain and other limbic regions, which correlate with negative symptoms as well (Strauss, Waltz, & Gold, 2014; Waltz et al., 2009). A disconnect in the system responsible for assigning rewards and context may explain the reduced ability of rewards and punishments to motivate behaviour in schizophrenia and lead to avolition and anhedonia (Maia & Frank, 2017). In the current tasks, these abnormal systems presented in a social context, indicating that abnormal learning from social rewards could easily explain social withdrawal as well as the other negative symptoms above.

8.1.1. Strengths and limitations

A particular strength of our approach is the implementation of a clear definition of extreme high/low schizotypy traits. Previous work has shown that the high end of the schizotypy continuum is at an increased risk for developing psychosis (Raine, 1991; Salokangas et al., 2013) thus the comparison of high vs low schizotypy implemented here can inform investigations of transition to psychosis at those at a particular early risk of transition. Furthermore, the neural and behavioural results reported here used CP (positive schizotypy subfactor scores) as a covariate. Thus, in comparison to previous work focusing mainly on the

positive symptoms of schizotypy (Debbané, Van der Linden, Gex-Fabry, & Eliez, 2009; Kerns, 2005; Modinos et al., 2018; Waltmann et al., 2019) here we show that total high schizotypy matches the findings of abnormal hierarchical (behavioural and neural) learning and abnormal processing of uncertainty observed in clinical samples (Adams et al., 2013; Cole et al., 2020; Corlett et al., 2007; Corlett et al., 2010; Corlett et al., 2009; Ermakova et al., 2018; Gradin et al., 2011; Murray et al., 2008; Pessiglione et al., 2006; Schultz et al., 1997). As such, investigations of high schizotypy are highly encouraged in the field to inform risk and protective factors of transition to clinical presentation. Similar to previous uses of these paradigms (Diaconescu et al., 2014; Sevgi, Diaconescu, Henco, Tittgemeyer, & Schilbach, 2020), our experimental design can be limited to level 1 of theory of mind inference (inferring the mental state of advisor) as advice was provided in the form of a social cue on screen removing the recursive nature of social inference (i.e. "I think what he thinks what I think" higher level theory of mind). This is not necessarily a disadvantage as it restricts the conclusions drawn from this study to a particular level of social inference and it meets the aims of the work (i.e. investigating whether hierarchical learning is abnormal in HS subjects as observed in clinical samples) and allows for straightforward application of efficient models like HGF. Yet, this approach limited the conclusions drawn from this study to a particular level of social cognition.

The belief updating task also had certain limitations. Due to scanning time constraints for the current project, we could only include 60 trials, with 15 events per interaction term. In comparison, previous work has generally included 88 trials with half being positive, half being negative (Garrett et al., 2014; Garrett & Sharot, 2017; Sharot et al., 2011; Sharot, Guitart-Masip, Korn, Chowdhury, & Dolan, 2012). While we did replicate the optimism bias observed in previous studies, the limited number of trials could have affected the power to detect group differences. However, we speculate the inclusion of more trials might not affect the behavioural

results as the literature suggests HS cohorts present with behaviourally similar performance to LS in social tasks (Kozhuharova et al., 2020). Another limitation relates to the lack of assessment of subjectively experienced estimation errors. While formally the estimation error with this type of task corresponds to the difference between participants' first estimate and the presented base rate in each trial, the participants may not perceive this difference as an indication that their initial judgement was erroneous because of personal vulnerabilities. For instance, a strong family history of cancer may suggest a higher personal risk of suffering from cancer relative to the general population base rate, so that a presentation for a lower population base rate may not be subjectively perceived as an error. Subjective experience of estimation errors needs to be assessed to improve the methodological precision of the paradigm.

8.1.2. Conclusions for social cognition in schizotypy samples

Despite these limitations, the current work presents a valuable contribution to the field. Compared to LS subjects, HS subjects showed greater activity in the vmPFC and the left IFG, and lower activity in the dlPFC, in response to social prediction errors (both negative and positive interaction conditions). These findings suggest that, in order to achieve the same behavioural performance as LS subjects, the prefrontal cortex is over activated in HS individuals particularly during self- and other- referential processing. Furthermore, socially salient estimation errors might trigger a more substantial effort to integrate social information into prior beliefs, compared to non-social estimation errors. Lower activity in the dlPFC in HS subjects for tracking social positive errors might suggest a problematic contextual representation for social events with good news. Finally, across individual task conditions we observed a widespread network of lower functional activity in the HS subjects in response to

prediction errors with main regions being the IFG, MFG and ventral striatum. These findings strongly suggest that high schizotypy is associated with a dysfunctional brain response during social prediction errors paralleling findings in schizophrenia patients. Using computational models, we further identified that HS subjects overestimate the volatility of the environment and are slower to learn from feedback about the global task/environment. We also observed a neural underweighting of both low-level PEs and high-level PEs in HS subjects, further suggesting that HS subjects suffer from abnormal hierarchical learning as observed in schizophrenia and clinical high risk. This abnormal learning from context can explain not only social abnormalities in schizotypy and schizophrenia, but also other observed cognitive biases. Overall, the results strongly suggest that future investigations of high schizotypy samples are much needed to provide a comprehensive developmental pathway from higher risk in the general population to frank clinical symptoms. Of particular importance, there is a need to investigate protective factors as the increased frontal activity in HS subjects seems to act as a compensatory mechanism allowing them to present with similar behavioural performance in the current tasks and a number of previous work as summarized in chapter 2.

8.2. MAM model findings and conclusions

Using resting state functional magnetic resonance imaging (rs-fMRI) and magnetic resonance spectroscopy (MRS) we carried out the first investigations of some of the key assumptions of the MAM animal model of psychosis in high schizotypy populations. The well-established MAM model provides a mechanistic explanation of how elevation in dopamine function leads to the generation of psychosis symptoms (Lisman, John, Grace, & Duzel, 2011). Crucially, administration of MAM leads to elevated striatal dopaminergic activity and over-activity in reciprocal signalling pathways between the MTL and striatum (Lodge & Grace, 2007). This overactivation stimulates GABAergic neurons projecting from the striatum to the

ventral pallidum leading to disinhibition of midbrain dopaminergic neurons and the increase in the release of dopamine in the striatum. In turn, the dopaminergic neurons in the midbrain project back to the striatum and the hippocampus, producing further disinhibition and forming a positive feedback loop (Hammad & Wagner, 2006).

The MAM animal model indicates that dysfunction of the GABAergic neurotransmitter system plays a major role in the pathophysiology of schizophrenia (Marín, 2012). The model suggests a link between disrupted cortical GABAergic function and the well-validated dysregulation of hippocampal dopaminergic signalling characteristic of schizophrenia (Grace, 2010). Research indicates that this dopaminergic hyperactivity is a consequence of the reduced number of parvalbumin inhibitory interneurons in the hippocampus and the PFC (Lodge & Grace, 2008; Lodge, Behrens, & Grace, 2009; Zhang, & Reynolds, 2002). Parvalbumin interneurons contain and release GABA that inhibits, or limits, the activity of pyramidal neurons, the neurons that provide the output of the hippocampus and prefrontal cortex (Grace, 2010). Indeed, studies revealed that MAM rats also show a selective loss of parvalbumin-containing interneurons in both the hippocampus and the prefrontal cortex (Lodge et al., 2009). Thus, the model advocates that people with an elevated risk of psychosis, or in the early stages of a psychotic disorder, would be expected to show, relative to healthy controls: decreased cortical GABA levels due to loss and dysfunction of inhibitory GABAergic interneurons, and abnormal hippocampal neural activity that leads to the dysregulation of striatal-midbrain dopamine signalling (Gomes & Grace, 2016; Lodge & Grace, 2011). The current thesis, for the first time, tested these specific assumptions of the MAM model in a sample of high schizotypy individuals, as they are conceded to represent the earliest increased risk for psychosis (Kwapil, Gross, Silvia, & Barrantes-Vidal, 2013; Raine, 1991; van Os, Linscott, Myin-Germeys, Delespaul, & Krabbendam, 2009).

Using resting state connectivity analysis, the current work found lower functional connectivity between the hippocampus and striatum and between hippocampus and thalamic regions (mainly the mediodorsal nucleus and midline thalamic nucleus) in healthy individuals with high levels of schizotypy traits compared to those with low levels. However, the HS and LS groups showed no difference in hippocampal – PFC connectivity. The findings suggest that abnormal hippocampal functional connectivity is characteristic of high schizotypy (i.e. SPQ total scores) rather than any subfactor alone. Furthermore, using 1H MRS, we found lower cortical levels of both GABA and glutamate metabolites in the mPFC in healthy individuals with high levels of schizotypy traits compared to those with low levels. Furthermore, resilience scores (measuring the ability to cope with stress) were found to moderate the effects of GABA in predicting schizotypy group (high, low). The odds of a participant with high GABA and high resilience scores being in the low schizotypy group were 1.18 higher than those with low GABA and low resilience scores. Thus, our results provide support for the key assumptions of the MAM model listed above, mainly abnormal hippocampal functioning and abnormal cortical GABA levels. Together, current and previous findings are in line with the broader schizophrenia literature and suggest that schizotypy samples present with similar abnormal neural signatures as those seen in clinical samples.

The presently observed reductions in hippocampal-striatum and hippocampal-thalamus connectivity at rest are in line with clinical high risk (CHR) and schizophrenia findings. Studies have reported that the hippocampus shows reduced functional connectivity with distributed brain regions during rest in schizophrenia (Liang et al., 2006; Zhou et al., 2007) including the bilateral putamen region within the striatum (Kraguljac, White, Hadley, Reid, & Lahti, 2014). Reduced resting state connectivity between the hippocampus and thalamus have also been reported in a large sample of schizophrenia patients compared to controls (Samudra et al., 2015). A recent study in a psychosis CHR cohort did report altered effective connectivity

between the hippocampus and the striatum, particularly in CHR subjects that subsequently went on to develop psychosis (Modinos et al., 2020). Our findings are also consistent with predictions from animal models of psychosis development (Howes et al., 2009b; Modinos, Allen, Grace, & McGuire, 2015) that propose hippocampal dysfunction and dysconnectivity play a key role in the symptomatology and progression of psychosis disorders (Gomes & Grace, 2016; Lodge & Grace, 2011). We also found reduced connectivity between the hippocampus and the thalamus, mainly the midline thalamic nucleus (although it spans across other thalamic nuclei as well; (Behrens et al., 2003). The midline thalamic nucleus specifically innervates the CA1 region of the hippocampus (Vertes, 2006) and could be a possible source of the observed increased hippocampal activity in schizophrenia (Allen et al., 2016; Allen et al., 2018; Schobel et al., 2009). PET studies also reveal less regional metabolic activity in the thalamus of schizophrenia patients compared to controls (Clark, Kopala, Li, & Hurwitz, 2001; Hazlett et al., 2004) and several studies have reported reduced volume of the thalamus in both patients (Ettinger et al., 2001) and schizotypy samples (Byne et al., 2001; Siever et al., 2002).

Our findings of reduced cortical GABA and glutamate are also consistent with the wider spectroscopy literature in the schizophrenia field. Lower medial prefrontal cortex (mPFC) GABA levels have been reported in schizophrenia patients compared to healthy controls (Chen et al., 2014; Goto et al., 2009; Marsman et al., 2011; Marsman et al., 2014; Rowland et al., 2016; Rowland et al., 2013) but see (Egerton, Modinos, Ferrera, & McGuire, 2017) for a review of inconsistent results). Studies investigating metabolite levels in CHR individuals have also found decreased GABA levels (Menschikov et al., 2016), but also increased levels (de la Fuente-Sandoval et al., 2016) or no differences in GABA levels between at-risk samples and healthy controls (Da Silva et al., 2019; Grent et al., 2018; Marenco et al., 2016; Modinos et al., 2018; Wang et al., 2016). Findings are further complicated by reports that in clinical-high risk individuals, medial prefrontal cortex GABA levels are negatively correlated with the severity

of negative symptoms (Modinos et al., 2018) and that unaffected siblings have significantly lower GABA levels compared with controls (Marenco et al., 2016). Yet, reduced cortical GABA levels, as reported here and in previous work with clinical samples, are consistent with MAM predictions for the mechanisms that lead to psychosis symptomatology. Cortical GABA levels should be decreased in psychosis due to loss and dysfunction of inhibitory GABAergic interneurons. Both the uptake (Reynolds, Czudek, & Andrews, 1990; Simpson, Slater, Deakin, Royston, & Skan, 1989) and release (Sherman, Davidson, Baruah, Hegwood, & Waziri, 1991) of GABA have been reported to be reduced in cortical synaptosomes prepared from schizophrenic subjects. In the PFC, the activity of glutamic acid decarboxylase, the synthetic enzyme for GABA, is reduced in subjects with schizophrenia (Mackay et al., 1982; Sherman et al., 1991) as is the expression of the mRNA for this enzyme (Akbarian et al., 1995; Huang & Akbarian, 2007). In addition, ligand binding studies have revealed abnormalities in PFC GABA receptors in schizophrenia (Benes, Vincent, Marie, & Khan, 1996). Furthermore, research has shown that the dopaminergic hyperactivity characteristic of schizophrenia is a consequence of the reduced number of parvalbumin inhibitory interneurons in the hippocampus and the PFC (Lodge & Grace, 2008; Zhang, & Reynolds, 2002). Parvalbumin interneurons contain and release GABA that inhibits, or limits, the activity of pyramidal neurons, the neurons that provide the output of the hippocampus and prefrontal cortex (Grace, 2010). Indeed, studies revealed that MAM rats also show a selective loss of parvalbumin-containing interneurons in both the hippocampus and the prefrontal cortex (Lodge et al., 2009). Decreases in parvalbumin expression might also affect certain classes of cortical GABA interneurons known to be reduced in schizophrenia populations (Akbarian et al., 1995). Thus, neurodevelopmental animal model of psychosis (Moore, Jentsch, Ghajarnia, Geyer, & Grace, 2006) indicates that mPFC dysfunction leads to increased functional loss of hippocampal parvalbumin interneuron (Gomes & Grace, 2017), which is associated with hippocampal

hyperactivity through disinhibition of glutamatergic pyramidal cells (Grace, 2010). The mPFC can regulate hippocampal and subcortical dopamine neuron activity via the nucleus reuniens of the thalamus (Zimmerman & Grace, 2016), thus the development of subcortical hyperdopaminergia in rodents has been linked to a failure of the mPFC to down-regulate medial temporal lobe activity (Gomes & Grace, 2017). The current findings of reduced mPFC GABA levels in high schizotypy subjects would be consistent with a diminished GABAergic regulation from the mPFC.

Further, we found a significant interaction between resilience scores (the ability to cope with stress and trauma) and GABA levels in predicting schizotypy group membership (high, low). The odds of a person with high cortical GABA and high resilience being in the low schizotypy groups are almost doubled that for those people with low GABA and low resilience. The results support previous notions about the role of stress in the progression to psychosis, as a predisposition to deal with environmental stressors seems to lead to lower schizotypy scores whereas a higher stress sensitivity is associated with high schizotypy presentation (Zimmerman, Bellaire, Ewing, & Grace, 2013). In rats, exposure to stress during gestation induces marked changes in the behaviour of the offspring that are reminiscent of the positive, negative and cognitive symptoms present in schizophrenia (Koenig et al., 2005; Lemaire, Koehl, Le Moal, & Abrous, 2000). Several lines of evidence point to schizophrenia as a neurodevelopmental disorder in which stress or environmental insults during pregnancy or in early-life contribute to the onset of the disease by altering epigenetic DNA marking preferentially at cortical and hippocampal GABAergic neurons (Benes et al., 2011; Fatemi et al., 2008; Guidotti et al., 2011; Markham & Koenig, 2011; Roth, Lubin, Sodhi, & Kleinman, 2009; Zhang et al., 2010). Further work in animals shows that the introduction of pre- and/or postnatal stress by injecting rats with corticosterone leads particularly to decreases of mRNA for GAD67, the enzime that synthesises GABA (Deslauriers, Larouche, Sarret, & Grignon,

2013; Giovanoli et al., 2013; Stone et al., 2001). Thus, early stress perturbs the development of GABA neurons, which migrate over extensive distances to reach their final location in the hippocampus. This makes them more vulnerable than interneurons in other cortical regions to stressors (Tricoire et al., 2011). Studies further suggest that perinatal oxidative-stress mechanisms produce an alteration in the normal development of parvalbumin interneurons which is already evident during adolescence (Powell, Sejnowski, & Behrens, 2012). The decreased expression of parvalbumin in synaptic terminals leads to increased asynchronous GABA release from parvalbumin interneurons (Manseau et al., 2010). As discussed earlier, alterations in parvalbumin expression are consistently observed in schizophrenia. Taken together, the findings suggest that stress during the maturation window for parvalbumin interneurons may, by alteration of normal brain development, lead to the emergence of schizophrenia-like behavioural dysfunctions when subjects reach early adulthood (Powell et al., 2012). Another important component to the stress response is the increased release of dopamine that occurs in the medial prefrontal cortex (Benes, & Berretta, 2001). An increase of dopamine forming appositions within interneurons has been induced by exposing rats both pre- and postnatally to stress-related doses of corticosterone (Benes, 1997). Thus, it is possible that the postnatal maturation of GABA cells in the cortex may be normally influenced by the ingrowth of dopamine fibers, but abnormally affected when this occurs in individuals for whom pre- and postnatal stress are co-morbid factors. In this latter case, it would have to be assumed that gene(s) involving the dopamine system and perhaps also cortical GABA cells would be affected by prenatal exposure to stress and would be permanently sensitized in such individuals (Benes, & Berretta, 2001). The current findings show that individuals at increased risk for schizophrenia do present with reduced GABA levels only when subjects are not able to cope with environmental trauma, supporting the notion that stress at the developmental stages might lead to abnormalities in the neural inhibitory system. Thus, the ability to cope with

environmental stress and trauma seem to act as a protective factor on the GABAergic system leading to lower schizotypy scores.

Cortical glutamate levels in the current study were found to be significantly reduced in high schizotypy compared to low schizotypy individuals, a finding consistent with some schizophrenia research (Goto et al., 2009; Marsman et al., 2013; Stan et al., 2015; Yoon et al., 2010) and some work with CHR samples (Egerton et al., 2014; Lutkenhoff et al., 2010). Dysfunction of the glutamatergic system has also been implicated as a possible mechanism leading to psychosis and the neural brain volume changes observed in schizophrenia (Marsman et al., 2013). The glutamatergic system might affect synaptic plasticity and cortical microcircuitry, in particular (N-methyl-D-aspartate) NMDA-receptor signalling (Harrison & Weinberger, 2005). NMDA-receptors are glutamate-gated ion channels, which play an important role in excitatory neurotransmission, plasticity, and excitotoxicity (Cull-Candy, Brickley, & Farrant, 2001; Paoletti & Neyton, 2007). Depending on the severity and duration of the NMDA-receptor hypofunction state, postsynaptic neurons can develop morphological changes and may cause chronic psychosis and structural brain changes similar to those associated with psychosis (Kondziella, Brenner, Eyjolfsson, & Sonnewald, 2007; Olney, Newcomer, & Farber, 1999; Stone, Morrison, & Pilowsky, 2007). In healthy subjects, acute administration of the non-competitive NMDA antagonist ketamine specifically selects NMDA receptors and the alteration in NMDA transmission results in a significant increase in dopamine release, comparable to the increased dopamine observed in schizophrenia patients (Kegeles et al., 2000). This observation confirms in humans a regulation of dopaminergic responses by glutamatergic inputs as observed in rodents (Becker et al., 2003; Miller, & Abercrombie, 1996) and indicates that the acute hyper-response of dopaminergic neurons is not solely determined by the availability of dopamine stores in the terminals, but also by the regulation of dopaminergic neurons through glutamatergic transmission. The PFC regulates (partly via

NMDA receptors) subcortical dopamine through glutamatergic projections to the midbrain dopaminergic neurons providing a model for cortical-subcortical dysconnectivity potentially relevant to the pathophysiology of the illness (Frohlich & Van Horn, 2014).

8.2.1. Implications of the findings for transition and symptomatology

Mediated by connectivity in a hippocampal–midbrain-striatal circuit, one consequence of abnormal hippocampal activity is a sustained increase in extrasynaptic DA release throughout midbrain and striatal regions (Blaha, Yang, Floresco, Barr, & Phillips, 1997; Gomes & Grace, 2017; Legault & Wise, 1999; Lodge & Grace, 2011; Peleg-Raibstein & Feldon, 2006). Indeed, midbrain dopamine neurons receive indirect inputs from the hippocampus and the frontal cortex (Lodge & Grace, 2011) and dopamine signalling is linked to aberrant salience in schizophrenia (Howes, & Nour, 2016; Kapur, 2003; Roiser et al., 2009; White, Joseph, Francis, & Liddle, 2010). Midbrain dopamine neurons respond to unexpected reward (Schultz, Dayan, & Montague, 1997) and under the condition of abnormally high hippocampal drive of dopamine neuron population activity, the dopaminergic system would be rendered hyper-responsive to phasic stimuli. Under such a state, all stimuli, whether threatening, rewarding, or benign, would cause a maximal phasic activation of the dopamine system (Grace, 2010; Grace, 2010). Therefore, there would be a mismatch between the actual behavioural salience of the object, and the much greater salience that is attributed by the dopaminergic response. As a result, all stimuli would be treated as one that requires maximal attention and reaction; a state that has been termed aberrant salience (Kapur, 2003). This aberrant salience is thought to generate a distorted model of the environment founded on erroneous inference (Corlett, Frith, & Fletcher, 2009) and is proposed to occur during the prodromal phase preceding frank psychosis. In other words, phasic dopamine release signals reinforcement prediction errors, any large stochastic fluctuation in dopamine release may disrupt learning about stimulus–

reinforcement associations, generating a state in which motivational salience could be misattributed to neutral stimuli and likely leads to abnormal updating of beliefs about the environment (Kapur, 2003). Thus, hippocampal hyperactivity leading to striatal dopamine dysregulation might be a neural pathway that leads to aberrant salience (Heinz, 2002; Kapur, 2003; Radua et al., 2015). Previous neuroimaging studies of motivational and reward salience processing also suggest salience dysregulation and altered activation within a hippocampal–striatal–midbrain network in people at CHR for psychosis (Ermakova et al., 2018; Millman et al., 2019; Modinos et al., 2020; Roiser et al., 2009; Roiser, Howes, Chaddock, Joyce, & McGuire, 2013; Schmidt et al., 2017; Smieskova et al., 2015; Winton-Brown et al., 2017). Aberrant salience has also been observed in schizotypy samples(Cicero, Becker, Martin, Docherty, & Kerns, 2013; Roiser et al., 2013). Across two experiments testing allocation of attention to cues that have predictive significance, individuals scoring high on schizotypy psychometric measures demonstrated abolitions of the effects of relevance that were otherwise sustained in individuals low on these traits (Haselgrove et al., 2016). The current results, by reporting abnormal hippocampal connectivity within a medial temporal area, support the notion that this brain region is impaired in samples at the earliest risk for psychosis. Combined with previous work showing aberrant salience in the same risk category (Cicero et al., 2013; Haselgrove et al., 2016; Roiser et al., 2013) the current results present a convincing case that the hippocampal abnormalities associated with progression of schizophrenia from the premorbid through the prodromal stages of syndromes (Allen et al., 2012; Lisman et al., 2008; Lodge & Grace, 2008; Mechelli et al., 2011; Moore et al., 2006; Pantelis et al., 2003; Schobel et al., 2013; Valli et al., 2011) are already present in HS samples.

As a consequence of reduced number of cortical parvalbumin-containing interneurons, one of the most consistent findings from postmortem studies in schizophrenia is a reduction in the GABA-synthesizing enzyme, GAD67 mRNA and associated decrease in GAD-67 protein

(Akbarian et al., 1995; Hashimoto et al., 2003; Volk, Austin, Pierri, Sampson, & Lewis, 2000). The potential effects of a reduction in GAD67 on cortical excitatory/inhibitory networks is a key component in some neurobiological models of schizophrenia (Maric, Piantadosi, & Floresco, 2015). GABA dysfunction is thought to lead to the disinhibition of glutamatergic pyramidal neurons and a loss of synchronous cortical activity (Lewis, Curley, Glausier, & Volk, 2012; Lisman et al., 2008). Because cortical gamma oscillations require the strong and synchronous inhibition of networks of pyramidal neurons (reviewed in (Gonzalez-Burgos & Lewis, 2008), deficient GABA neurotransmission in the PFC has been hypothesized to contribute to altered gamma oscillations and impaired cognition in schizophrenia (Gonzalez-Burgos, Fish, & Lewis, 2011; Lewis, Hashimoto, & Volk, 2005; Lewis et al., 2012; Lisman, 2012; Lisman et al., 2008), such as emotional processing (Keefe, Eesley, & Poe, 2005). Consistent with this interpretation, manipulations in animal models that reduce GABA-mediated inhibition diminished gamma oscillations (Lodge et al., 2009) and impaired cognitive function (Enomoto, Maric, & Floresco, 2011; Gruber et al., 2010; Paine, Slipp, & Carlezon, 2011; Sawaguchi, Matsumura, & Kubota, 1989). In addition, in individuals with schizophrenia, negative modulation of GABAergic neurotransmission exacerbated symptoms (Ahn, Gil, Seibyl, Sewell, & D'souza, 2011), whereas positive modulation was associated with increased frontal lobe gamma oscillations during a cognitive control task (Lewis et al., 2008). There is evidence of impaired cognitive control in HS samples (see Steffens, Meyhöfer, Fassbender, Ettinger, & Kambeitz, 2018) for a meta-analysis) along with impaired neural response of brain regions supporting cognitive control (Kozhuharova et al., 2020; Modinos, Ormel, & Aleman, 2010). Combined with the current findings of reduced GABA in cortical regions, our findings, the results support the main predictions from the MAM model of psychosis progression.

In healthy people, NMDA-receptor antagonists, such as ketamine and phencyclidine (PCP), induce symptoms that mimic the positive and negative symptoms seen in schizophrenia

(Adams & Moghaddam, 1998; Adler et al., 1999; Coyle, Basu, Benneyworth, Balu, & Konopaske, 2012; Krystal et al., 1994; Lahti, Weiler, Michaelidis, Parwani, & Tamminga, 2001; Moghaddam, Adams, Verma, & Daly, 1997; Olney & Farber, 1995), as well the cognitive deficits characteristic of schizophrenia (Adler et al., 1999; Coyle et al., 2012; Krystal et al., 1994). A single dose of PCP has been shown to produce hallucinations and reduce cognitive function in schizophrenia patients (Krystal et al., 1994; Steinpreis, 1996). While both dopamine agonists (e.g. amphetamine) and glutamate non-competitive NMDA receptor antagonists (e.g. PCP) can replicate psychosis most effectively, the latter are able to better produce the negative and cognitive deficits associated with schizophrenia, including social cognition deficits. Several groups have been able to successfully show inhibition of social interaction, induced by NMDA-receptor antagonists in animals (Audet, Goulet, & Doré, 2009; Becker et al., 2003; Ellenbroek & Cools, 2000; Harich, Gross, & Bespalov, 2007; Qiao et al., 2001; Sams-Dodd, 1995; Silvestre, Nadal, Pallares, & Ferre, 1997; Slot, Kleven, & Newman-Tancredi, 2005; Snigdha & Neill, 2008; White, Minamoto, Odell, Mayhorn, & White, 2009). A number of social cognition deficits have also been observed in schizotypy samples (Aghvinian & Sergi, 2018; Cohen, Mohr, Ettinger, Chan, & Park, 2015; Ettinger et al., 2015), in line with animal models showing inhibition of social interaction induced by NMDA-receptor antagonists in animals. Thus, the current findings of reduced glutamate levels in high schizotypy individuals are in line with dysfunction of the glutamatergic system in psychosis and strongly suggest that abnormal glutamatergic system functioning is present in the early stages of risk to psychosis.

8.2.2. Limitations and future directions

Schizophrenia patients present with increased subcortical dopamine synthesis and release (Howes et al., 2009; Laruelle et al., 1996; Lindström et al., 1999; Mackay et al., 1982).

Elevated dopamine function in the striatum and the midbrain has also been documented in CHR populations, particularly in the subgroup that subsequently develops a psychotic disorder (Allen et al., 2012; Howes et al., 2011). However, in the current study it is challenging to confirm if the hippocampal-striatal abnormal connectivity is associated with abnormal dopamine signalling. Indeed, striatal dopamine activity in schizotypy has been scarcely investigated, although existing research suggests that individuals with high levels of schizotypy may benefit from DA agonists in terms of cognitive performance (Mohr & Ettinger, 2014). Less is known about how altered dopamine signalling and/or dysconnectivity in networks that regulate dopamine function relate to behavioural models of symptom formation such as aberrant salience in schizotypy groups, although aberrant salience has been observed in schizotypy samples (Haselgrove et al., 2016; Roiser et al., 2013). Following from these findings, the reduced hippocampal – striatum connectivity observed here in HS subjects may be related to abnormal dopamine function that leads to the presentation of subclinical phenotypes, although much more work is needed to directly test this prediction.

Animal models of psychosis development propose hippocampal dysfunction and dysconnectivity results in perturbed striatal dopamine signalling (Howes et al., 2009; Modinos et al., 2015). There is significant literature demonstrating schizophrenia and CHR cohorts present with increased hippocampal resting activity, specifically increased regional cerebral blood flow and increased regional cerebral blood volume (Allen et al., 2015; Allen et al., 2018; Medoff, Holcomb, Lahti, & Tamminga, 2001; Schobel et al., 2009; Tamminga, Stan, & Wagner, 2010). Longitudinal studies in clinical high-risk groups showed that normalization of hippocampal resting cerebral blood flow tracked with clinical improvement of symptoms, while persistent abnormalities of hippocampal resting cerebral blood flow were characteristic of those who remained symptomatic or developed psychosis (Allen et al., 2015). Longitudinal follow-up in an CHR cohort showed that the onset of psychosis was associated with a

progressive increase in hippocampal cerebral blood volume (Schobel et al., 2009). This increased hippocampal neural activity is believed to lead to the dysregulation of striatal-midbrain dopamine signalling (Gomes & Grace, 2016; Lodge & Grace, 2011) through a hippocampal-striatal-midbrain circuit. Further, longitudinal studies in CHR groups showed that normalization of hippocampal resting cerebral blood flow tracked with clinical improvement of symptoms, while elevated hippocampal resting cerebral blood flow persisted in those who remained symptomatic or developed psychosis (Allen et al., 2015). Investigations of hippocampal regional cerebral blood flow and blood volume in high schizotypy samples have not been published to the best of our knowledge, and such work would be highly beneficial to allow for a comprehensive longitudinal view of the risk progression continuum.

The findings should be considered in light of the study's limitations, particularly the shortcoming of using MRS. The greatest asset of MR techniques is their noninvasiveness, the fact that both biochemical (spectroscopy) and spatial information (imaging) can be obtained without destroying the sample is obviously a great asset for in vivo studies. An additional advantage of MRS versus comparable techniques is the lack of ionizing radiation, which are required for other techniques such as computer-assisted tomography and positron emission tomography (Chatham & Blackband, 2001). Given the particular behavioral symptoms associated with schizophrenia-spectrum disorders (i.e. paranoia), MRS is a particularly useful tool to measure biochemical abnormalities. Yet, one limitation of 1H-MRS is that it measures total GABA concentrations within a relatively large voxel, which is determined a priori, and cannot discriminate between GABA levels in different cell types. This limits the application of 1H-MRS in addressing the cell- and network- specific GABA abnormalities hypothesized to occur in schizophrenia (Lewis et al., 2012). For this reason, the current findings cannot inform on the specific mechanisms that might lead to reduced GABA and glutamate levels and we cannot test whether these results are due to reduced GAD67 or reduced density of parvalbumin

interneurons, as suggested by animal models. The 1H-MRS GABA signal may reflect the entire GABA content of the voxel (that is, intracellular and extracellular, and involved in metabolism or neurotransmission). Recent work argues that the 1H-MRS GABA signal predominantly relates to extracellular, extra-synaptic GABA providing tonic inhibitory tone, rather than GABA involved in phasic synaptic neurotransmission (Dyke et al., 2017; Stagg, 2014). Theoretically, the 1H-MRS GABA signal should therefore be sensitive to GAD67 reduction, but we could not test this in the current study. Pharmacologically induced alterations in synaptic GABA may be more sensitively imaged with positron emission tomography (PET, (Egerton et al., 2017). In the future, combination of this approach with 1H-MRS in the same subjects, and potentially during the same scanning session on combined PET-magnetic resonance platforms, might investigate dysfunction of synaptic versus nonsynaptic GABA and glutamate in schizophrenia.

Finally, while the current findings are consistent with the abnormalities implicated in the development of schizophrenia by animal and post-mortem studies, it is challenging to link them to findings in clinical high-risk samples or schizophrenia patients. The inconsistencies reported in relation to both cortical glutamate and GABA levels in patients may be related to between-study and within-study variation in the age and the treatment history of the patients studied as has been reported in some individual studies (Kegeles et al., 2012; Marenco et al., 2016; Rowland et al., 2013; Rowland et al., 2016). For example, antipsychotic medication is likely to affect MRS measures of GABA as one study reported that GABA levels were significantly higher in patients taking typical antipsychotics than in those taking atypical antipsychotics with further negative correlations observed between cortical GABA levels and dose of antipsychotics (Tayoshi et al., 2010). Disease stage has also been strongly implicated in influencing the nature of the findings: for example, GABA levels in the basal ganglia appear to be reduced in patients in the early stage of psychosis, whereas increased GABA levels in the

anterior cingulate cortex and the parieto-occipital cortex have been reported in chronic patients (Egerton et al., 2017; Port & Agarwal, 2011). Similarly, illness stage has been implicated in glutamate abnormalities in schizophrenia such that elevated medial frontal Glx (the combined metabolite levels of glutamate, glutamine and GABA) were evident in individuals at high risk of developing psychosis but not in those with first-episode psychosis or chronic schizophrenia (Merritt, Egerton, Kempton, Taylor, & McGuire, 2016). Longitudinal studies investigating individuals at the full continuum of risk for psychosis are much needed to shed light on the developmental mechanisms of inhibitory and excitatory systems in the progression to psychosis.

8.2.3. Conclusions for the MAM model assumptions in schizotypy samples

The current thesis, for the first time, tested key assumptions of the MAM model of psychosis development in a sample of individuals scoring at the extreme high end of the schizotypy continuum, compared to individuals scoring at the low end of the schizotypy continuum. Previous work has shown that high scorers are at an increased risk of progression to psychosis (Kwapil et al., 2013; Raine, 1991; van Os et al., 2009). Thus, we tested if these individuals are already presenting with the key abnormalities involved in psychosis progression. The MAM model makes the specific predictions that individuals at risk will present with reduced cortical GABA and with abnormal hippocampal neural activity (Grace, 2010; Lodge & Grace, 2011; Modinos et al., 2015). We found that high schizotypy individuals, in comparison to low schizotypy, present with reduced resting state hippocampus-striatum and hippocampus-thalamus connectivity and reduced cortical GABA. Thus, our results strongly indicate that, despite being healthy individuals from the general population, high schizotypy is characterised by a neural profile of abnormalities similar to those seen in clinical high risk and

consistent with animal models of transition to psychosis. Thus, high schizotypy individuals are a highly valuable sample to test in order to develop a comprehensive model of psychosis progression risk and protective factors that could affect transition from high schizotypy to clinical high risk. Likewise to work in clinical high risk and schizophrenia, the current findings also suggest that abnormal hippocampal neural activity could provide a mechanistic explanation of the aberrant salience observed in schizotypy. The reduced cortical GABA reported here could similarly provide an explanation for the impaired cognitive control observed in high schizotypy samples, as deficient GABA population in the prefrontal cortex leads to altered gamma oscillations and the impaired cognitive control observed in schizophrenia. Our results also support the key role of stress in the progression to psychosis, as ability to cope with stress combined with higher cortical GABA predicted lower schizotypy scores. Early stress has been shown to perturb the development of GABA neurons and could lead to emergence of schizophrenia-like symptomatology in early adulthood (Powell et al., 2012). The reduced cortical glutamate levels suggest abnormalities of the NMDA receptor signalling in high schizotypy populations. NMDA abnormalities have been shown to produce not only positive symptoms, but also the negative and cognitive symptomatology observed in schizophrenia, including inhibition of social interactions.

In summary, high schizotypy individuals present with a neural profile matching the predictions of the MAM animal model of psychosis and indicating that abnormal hippocampal activity and reduced cortical GABA metabolite levels are already present in these populations, potentially explaining the presence of aberrant salience and impaired cognitive control in behavioural tasks. The reduced glutamate levels further support the notion that high schizotypy, similarly to clinical high risk and schizophrenia patients, present with abnormal NMDA receptor functioning leading to further symptom development, such as social inhibition. The implementation of high schizotypy samples , particularly, those scoring on the extreme high

end of the continuum, is strongly encouraged in order to develop comprehensive models of risk and protective factors in psychosis development, before the occurrence of frank clinical symptomatology.

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Appendixes

Ethics statement

The research for this project was submitted for ethics consideration under the reference PSYC 18/ 307 in the Department of Psychology and was approved under the procedures of the University of Roehampton's Ethics Committee on 10.10.18.

MRI Roehampton Information Form

Roehampton MRI information sheet

The information overleaf is intended to make sure you understand the nature of the MRI scanner that is being used in the experiment in which you have been asked to participate.

The experiment is being run by staff from University of Roehampton but the scanning takes place at Royal Holloway University of London and this information has been provided by them.

The information includes a screening form that anyone who is going to be scanned has to complete. It contains information on health conditions that mean that some people cannot be scanned. The form is administered and signed at Royal Holloway and is included here for information only. Please make sure you read it beforehand so that you know the necessary information before you arrive at the scanner.

Getting to the scanner

The MRI lab is on the Royal Holloway campus, Egham Hill, Egham, see the information:

http://www.rhul.ac.uk/aboutus/ourcampus/gettinghere.aspx

The Royal Holloway campus is a 15-20 walk. Please allow at least half an hour to get to the scanner from the station. It is very important that participants are punctual.

There is dedicated parking for participants close to the scanner or ask Ari, the technician for a parking permit.

The scanner is next to the Psychology department (Wolfson building). The phone number for the control room is 01784 414 429 - this gets through to Ari, the MRI technician.

When you arrive at the scanner, the door to the unit will be unlocked and you then need to press the buzzer to be allowed into the control room.

ROYAL HOLLOWAY, UNIVERSITY OF LONDONMAGNETIC RESONANCE IMAGING UNIT

INFORMATION FORM

These notes give some information about an fMRI study in which you are invited to take part.

FMRI is a method for producing images of the activity in the brain as people carry out various mental tasks. It involves placing the participant inside a large, powerful magnet which forms part of the brain scanner. When particular regions of the brain are active, they require more oxygen, which comes from red corpuscles in the blood. As a result, the flow of blood increases. This can be detected as changes in the echoes from brief pulses of radio waves. These changes can then be converted by a computer into 3D images. This enables us to determine which parts of the brain are active during different tasks.

As far as we know, this procedure poses no direct health risks. However, the Department of Health advises that certain people should NOT be scanned. Because the scanner magnet is very powerful, it can interfere with heart pacemakers and clips or other metal items which have been implanted into the body by a surgeon, or with body-piercing items. If you have had surgery which may have involved the use of metal items you should NOT take part. You will be asked to remove metal from your pockets (coins, keys), remove articles of clothing which have metal

fasteners (belts, bras, etc), as well as most jewellery. Alternative clothing will be provided as necessary. Watches and credit cards should not be taken into the scanner since it can interfere with their operation. You will be asked to complete a questionnaire (the Initial Screening Form) which asks about these and other matters to determine whether it is safe for you to be scanned. You will also be asked to complete a second, shorter, screening form immediately before the scan.

To be scanned, you would lie on your back on a narrow bed on runners, on which you would be moved until your head was inside the magnet. This is rather like having your head put inside the drum of a very large front-loading washing machine. The scanning process itself creates intermittent loud noises, and you would wear ear-plugs or sound-attenuating headphones. We would be able to talk to you while you are in the scanner through an intercom. If you are likely to become very uneasy in this relatively confined space (suffer from claustrophobia), you should NOT take part in the study. If you do take part and this happens, you will be able to alert the experimenters by activating an alarm and will then be removed from the scanner quickly. It is important that you keep your head as still as possible during the scan, and to help you with this, your head will be partially restrained with padded headrests. We shall ask you to relax your head and keep it still for a period that depends on the experiment but may be more than one hour, which may require some effort on your part. If this becomes unacceptably difficult or uncomfortable, you may demand to be removed from the scanner.

You may be asked to look at a screen through a small mirror (or other optical device) placed just above your eyes and/or be asked to listen to sounds through headphones. You may be asked to make judgements about what you see or asked to perform some other kind of mental task. Details of the specific experiment in which you are invited to participate will either be

appended to this sheet or else given to you verbally by the experimenter. Detailed instructions will be given just before the scan, and from time to time during it.

The whole procedure will typically take about 1 hour, plus another 15 minutes to discuss with you the purposes of the study and answer any questions about it which you may raise. You will be able to say that you wish to stop the testing and leave at any time, without giving a reason. This would not affect your relationship with the experimenters in any way. The study will not benefit you directly, and does not form part of any medical diagnosis or treatment. If you agree to participate you will be asked to sign the initial screening form that accompanies this information sheet, in the presence of the experimenter (or other witness, who should countersign the form giving their name and address, if this is not practical). It is perfectly in order for you to take time to consider whether to participate, or discuss the study with other people, before signing. After signing, you will still have the right to withdraw at any time before or during the experiment, without giving a reason.

The images of your brain will be held securely and you will not be identified by name in any publications that might arise from the study. The information in the two screening forms will also be treated as strictly confidential and the forms will be held securely until eventually destroyed. Only the main investigator and the project supervisor will have access to your data.

The study involves the recording of typical brain function. Since we are only studying healthy volunteers, there is no intended clinical benefit to you from taking part in this study. The scans are not intended to provide a medical diagnosis or a clean 'bill of health' – and the person conducting your scans will not be able to comment on the results of your scans. The researchers involved do not have expertise in MRI diagnosis, as they are psychologists or allied scientists and are not doctors. We ask you to give the name and address of your Family Doctor. This is because occasionally, when we image healthy participants, the researchers may be concerned

that a potential abnormality may exist on the scan. In such case, we will send a copy of the image to your Family Doctor, so that they can decide what course of action is best. By signing the consent form, you authorize us to do this. If you are not willing to authorize this, you will not be able to participate in the study. It is important that you realize that these research scans are NOT a medical screening procedure, and will not provide any information that may help in the diagnosis of any medical condition. If you do have any health concerns, you should contact a qualified medical practitioner in the normal way.

Further information about the specific study in which you are invited to participate may have been appended overleaf, if the experimenter has felt that this would be helpful. Otherwise, he/she will already have told you about the study and will give full instructions prior to the scan. Please feel free to ask any questions about any aspect of the study or the scanning procedure before completing the initial screening form.

ROYAL HOLLOWAY, UNIVERSITY OF LONDON

MAGNETIC RESONANCE IMAGING UNIT

INITIAL SCREENING FORM

NAME OF PARTICIPANT ……

Sex: M / F

Date of birth……

Approximate weight in kg……. (one stone is about 6.3 kg)

Please read the following questions CAREFULLY and provide answers. For a very small number of individuals, being scanned can endanger comfort, health or even life. The purpose of these questions is to make sure that you are not such a person.

You have the right to withdraw from the screening and subsequent scanning if you find the questions unacceptably intrusive. The information you provide will be treated as strictly confidential and will be held in secure conditions.

Delete as appropriate

1. Have you been fitted with a pacemaker or artificial heart valve? YES/NO

2. Have you any aneurysm clips or shunts in your body, or a cochlear implant? YES/NO

3. Have you ever had any metal fragments in your eyes? YES/NO

4. Have you ever had any metal fragments, e.g. shrapnel in any other part of your body? YES/NO

5. Have you any surgically implanted metal in any part of your body, other than dental fillings and crowns (e.g. joint replacement or bone reconstruction)? YES/NO

6. Have you ever had any surgery that might have involved metal implants of which you are not aware? YES/NO

7. Do you wear a denture plate or brace with metal in it? YES/NO

8. Do you wear a hearing aid? YES/NO

9. Do you use drug patches attached to your skin? YES/NO

10. Have you ever suffered from any of: epilepsy, diabetes or thermoregulatory problems? YES/NO

11. Have you ever suffered from any heart disease? YES/NO

12. Is there any possibility that you might be pregnant? YES/NO

13. Have you been sterilised using clips? YES/NO

14. Do you have a contraceptive coil (IUD) installed? YES/NO

15. Are you currently breast-feeding an infant? YES/NO

Please enter here the name and address of your doctor (general practitioner):

I have read and understood the questions above and have answered them correctly.

SIGNED…… DATE……

In the presence of ……

(Name) ……. (signature)

Address of witness, if not the experimenter:

Participant Consent Form

University of Roehampton London

PARTICIPANT CONSENT FORM

Title of Research Project: Investigating cognitive processes during social interactions

Ethics reference N: PSYC 18/ 307

Brief Description of Research Project, and What Participation Involves:

You are being invited to take part in a research project. Before you decide if you want to participate, it is important for you to fully understand why the research is being done and what it will involve. Please take time to read this consent form carefully. If there is anything you do not understand, or if you would like more information, please feel free to ask any questions.

What is the purpose of the study?

We are interested in how the brain responds to different types of information (e.g. reactions to a probe or integrating social information) and how this may differ depending on various levels of personality traits. To do this we will use Functional Magnetic Resonance Imaging (FMRI) and Magnetic Resonance Spectroscopy (MRS) to explore which regions of the brain are utilised when we process these types of information. We hope that the results of this study may improve our understanding of how the brain processes and learns from social interactions.

Do I have to take part?

No. It is up to you to decide whether to take part and you are free to withdraw at any time without giving a reason. There is no compulsion or academic pressure to take part in this project and if you decline to participate or subsequently withdraw your course marks or any other academic activity will not be adversely affected.

Why have I been chosen?

In this study we are interested in studying up to 50 right-handed healthy people, between the ages of 18 and 65. You have been selected to participate in this study because you have participated in a previous study investigating social interactions (online study) and you meet the criteria for inclusion (based on your answers on demographics questions such as medical history, metal in your body, etc.).

What will the study involve?

The study will involve a single session outlined below:

We will ask you to:

- Come to the Combined Universities Brain Imaging Centre (CUBIC), which is located at Royal Holloway College, Egham.
- Complete a standardised MRI screening.
- During the Magnetic Resonance Imaging (MRI) session we will acquire a structural scan of your brain and carry out a number of functional scans during rest and while completing three separate tasks. During the resting scan all you need to do is watch a cross on the screen and let your mind wander (i.e. do not focus on anything in particular).

- We will ask you to do 2 separate tasks in the scanner, all of which investigate social interactions and the way in which people think about their environment. The first task (approximately 22 minutes) will ask you to estimate the likelihood of everyday events happening to you. The second task (approximately 22 minutes) will ask you to play a social guessing card game. On each trial you will be asked to choose a winning card after another player gives you advice.

- Before we start each task, we will make sure you are happy with the instructions and comfortable with the task. The functional tasks should not take more than 45 minutes to complete.

- Once the functional tasks are completed we will carry out the Magnetic Resonance Spectroscopy (MRS) scans. During the MRS scans all we ask you to do is relax and keep as still as possible. We will collect a single MRS scan lasting approximately 10 minutes in duration. MRS measures the concentration of brain metabolites in the examined tissue.

- The total time you will be in the scanner should not be more than approximately 85 minutes.

- Once the scan is finished you will be escorted back to the control room and invited to complete 4 questionnaires measuring anxiety and personality traits. These are standard questionnaires asking how you are doing, but do not ask for any specific information about your private life. Some of these questionnaires are of a sensitive nature relating to everyday feelings you might be experiencing. If you are unhappy answering these questions please let the researcher know now. You will also be asked to complete 2 brief tasks outside of the scanner. One of these tasks will take approximately 2 min and

is an attentional control task. The other will take approximately 17 min and is again a social guessing card game.

- We anticipate that the total time you will spend at CUBIC will be approximately 3.30 hours.

What is an FMRI scan?

Functional MRI is a totally safe, non-invasive procedure that uses strong magnetic fields to look at your brain (this type of scan does not involve the use of any ionising radiation [x-rays]). During the scan you will be lying inside a long, quite narrow tube (so it is important that you are not claustrophobic). Reflecting mirrors, mounted on a plastic surround, are fitted in a position that allows you to view a screen placed at the back of the scanner. It is on this screen that we will present the risky decision task. The scans are quite noisy, so we give you ear protection and we also give you an alarm call (a soft rubber bulb) you can squeeze at any time if you are feeling uncomfortable or want to be removed from the scanner. A fully trained CUBIC scan operator will go through the MRI screening form before you go into the scanner to make sure you are safe to enter the magnetic environment. The researchers and scan operator will be able to see you throughout the duration of the scan and will talk to you at regular intervals. Please, on the day of the scan wear comfortable clothes with minimal metal buttons or buckles.

What are the risks and benefits?

All MRI procedures will be conducted in accordance with the rigorous safety procedures in place at CUBIC, and therefore do not pose any significant risk. Prior to scanning you will be asked to complete a standardised safety screening form to ensure you have no contra-indications for MR imaging. Some people may find the space limitation in the scanner

unpleasant, but you will be given the opportunity to view the scanner before the study starts. The scans are quite noisy, so we give you ear protection which you will need to wear throughout the duration of the scan and we also give you an alarm button (a soft rubber bulb) you can squeeze at any time if you are feeling uncomfortable or want to be removed from the scanner.

CUBIC is wholly research orientated. As such, brain images acquired there are for specific research purposes only and are not suitable for diagnostic opinions. However, although not diagnostic scans, in the unlikely event of a possible structural abnormality being noted incidentally, we will contact your GP by letter. You will not be allowed to take part in the study unless you consent for us to contact your GP AND provide us with your current GP contact details.

What if there is a problem?

You will be given the contact details of the lead investigator involved in the study (details are included in the Debrief form), and you will be able to contact them if you have any concerns during your participation in the study. If you wish to complain about any aspect of the way you have been approached or treated during the course of this study, you should contact Dr James Gilleen. Alternatively, you may wish to contact Dr Diane Bray (Psychology, Head of Department). Contact details for both are included on the Debrief form.

Will my taking part in the study be kept confidential?

All the information about your participation in this study will be kept strictly confidential. Your results will be coded with a participant number and no personal information will be attached to the data. This anonymisation will occur at the earliest point of data collection. Data will be stored on a University computer for 10 years, while personal details will be stored separately in a locked filing cabinet. Only the named researchers and responsible individuals

from the University of Roehampton will have access to this data. The overall results of the study may be published in scientific journals. However, all personal data will remain confidential, and no data relating to individual participants will be published. In the unlikely event of a possible structural abnormality being noted incidentally, we will contact your GP by letter.

Responsible members of the University of Roehampton may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations. All will have a duty of confidentiality to you as a research participant.

What will happen to the results of the research study?

The results of this study may be published in scientific journals. However, no information which could be used to identify any individual participant will be published. If you are interested in finding out about the results of this research, please let us know, and we will make arrangements to inform you once the study is completed.

Main Investigator Contact Details:

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Consent Statement:

I confirm that I have read the Information sheet for participants.

I understand the aims and procedures of the study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily by the investigator. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time, without giving any reason. Although if I do so I understand that my data might still be used in a collated form. ☐

I have also been told that all these individuals have a duty of confidentiality to me as a research participant. ☐

I agree to take part in this research, and am aware that I am free to withdraw at any point without giving a reason, although if I do so I understand that my data might still be used in a collated form. I understand that the information I provide will be treated in confidence by the investigator and that my identity will be protected in the publication of any findings, and that data will be collected ☐

and processed in accordance with the Data Protection Act 1998 and with the University's Data Protection Policy.

I am happy to be contacted in the future about participation in other studies (though there is no obligation for me to take part and I can request that I am no longer to be contacted at any time.

Participant name (Please print clearly) …….

Signature ……

Date ……

I confirm that the aims and procedures of the experiment and any risks to the participant have been adequately explained to the participant whose signature I witness. In my opinion he/she appears to understand and wishes to participate.

Investigator name (Please print clearly) …….

Signature……

Please note: if you have a concern about any aspect of your participation or any other queries please raise this with the investigator. However, if you would like to contact an independent party please contact the Project supervisor, Director of Studies or Head of Psychology.

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Participant number: _____

Demographics Questionnaire

1	**Identifying gender**	**Male** **Female**
2	**Date of Birth**	
3	**Age**	
4	**Ethnicity**	**1) White British** **2) White Other** **3) Black of African American** **4) Latino/Hispanic** **5) Caribbean** **6) South Asian** **7) East Asian** **8) Mixed** **9) Prefer not to say**
5	**Ethnic generation**	**1) Born and raised abroad? If yes, where?** **2) Born and raised in the UK to parents who themselves were not born in the UK?** **3) Born and raised in the UK to parents who were also born and raised in the UK?**
6	**Highest Level of Education**	**1) Less than high school degree** **2) High school graduate (high school diploma or equivalent including GED)** **3) Some college but no degree** **4) Associated degree in college (2-year)** **5) Bachelor's degree** **6) Master's degree** **7) Doctoral degree** **8) Professional degree (JD, MD)**
7	**Work Status**	**1) Working (paid employee)** **2) Working (self-employed)** **3) Not working (temporary layoff from a job)** **4) Not working (looking for work)** **5) Not working (disabled)** **6) Student** **7) Prefer not to say**
8	**Marital Status**	**1) Married** **2) Widowed** **3) Divorced** **4) Separated** **5) Never married**
9	**What is your native language?**	
10	**Do you take recreational drugs?**	**Name:** **Frequency:** **Name:** **Frequency:** **Name:** **Frequency:** If you are not taking any recreational drugs at the moment, have you ever used any recreational drugs? If yes, please provide details.

11	**Do you have a history of any neurological or psychiatric conditions? If yes, can you please provide details?**	**1) No** **2) Yes (if yes, can you please provide details)**
12	**Are you currently taking any prescribed medication?**	**1) No** **2) Yes (if yes, can you please provide details)**
13	**How many units of alcohol would you say you consume on average per week?**	
14	**Do you have any metal in your body? If yes, please provide details.**	**1) No** **2) Yes (if yes, can you please provide details)**

Participant Number: _____

Paranoia Scale

Please read the following statements. To the right of each you will find five numbers, ranging from "1" (Not at all applicable) on the left to "5" (Extremely applicable to me) on the right. Circle the number which best indicates your feelings about that statement. For example, if a statement is not at all applicable to you circle "1". If you are neutral, circle "3", and if the statement is strongly applicable to you circle "5", etc.

	Not at all applicable to me				Extremely applicable to me
1. Someone has it in for me.	1	2	3	4	5
2. I sometimes feel as if I'm being followed.	1	2	3	4	5
3. I believe that I have often been punished without cause.	1	2	3	4	5
4. Some people have tried to steal my ideas and take credit for them.	1	2	3	4	5
5. My parents and family find more fault with me than they should.	1	2	3	4	5
6. No one really cares much what happens to you.	1	2	3	4	5
7. I am sure I get a raw deal from life.	1	2	3	4	5
8. Most people will use somewhat unfair means to gain profit or advantage, rather than lose it.	1	2	3	4	5
9. I often wonder what hidden reason another person may have for doing something nice for you.	1	2	3	4	5
10. It is safer to trust no one.	1	2	3	4	5
11. I have often felt that strangers were looking at me critically.	1	2	3	4	5
12. Most people make friends because friends are likely to be useful to them.	1	2	3	4	5
13. Someone has been trying to influence my mind.	1	2	3	4	5
14. I am sure I have been talked about behind my back.	1	2	3	4	5
15. Most people inwardly dislike putting themselves out to help other people.	1	2	3	4	5
16. I tend to be on my guard with people who are somewhat friendlier than expected.	1	2	3	4	5
17. People have said insulting and unkind things about me.	1	2	3	4	5
18. People often disappoint me.	1	2	3	4	5
19. I am bothered by people outside, in cars, in stores, etc., watching me.	1	2	3	4	5
20. I have often found people jealous of my good ideas just because they had not thought of them first.	1	2	3	4	5

Participant Number: _____

BDI-SF

Please circle the number beside the statement in each group that best described the way you have been feeling in the past week, including today.

1. 0 I do not feel sad.
   1 I feel sad.
   2 I am sad all the time and I cannot snap out of it.
   3 I am so sad or unhappy that I cannot stand it.

2. 0 I am not particularly discouraged about the future.
   1 I feel discouraged about the future.
   2 I feel I have nothing to look forward to.
   3 I feel that the future is hopeless and that things cannot improve.

3. 0 I do not feel like a failure.
   1 I feel I have failed more than the average person.
   2 As I look back on my life, all I can see is a lot of failure.
   3 I feel I am a complete failure as a person.

4. 0 I get as much satisfaction out of things as I used to.
   1 I do not enjoy things the way I used to.
   2 I do not get real satisfaction out of anything anymore.
   3 I am dissatisfied or bored with everything.

5. 0 I do not feel particularly guilty.
   1 I feel guilty a good part of the time.
   2 I feel quite guilty most of the time.
   3 I feel guilty all of the time.

6. 0 I do not feel disappointed in myself.
   1 I am disappointed in myself.
   2 I am disgusted with myself.
   3 I hate myself.

7. 0 I do not have any thoughts of killing myself.
   1 I have thoughts of killing myself, but I would not carry them out.
   2 I would like to kill myself.
   3 I would kill myself if I had the chance.

8. 0 I have not lost interest in other people.

1 I am less interested in other people than I used to be.
2 I have lost most of my interest in other people.
3 I have lost all of my interest in other people.

9. 0 I make decisions about as well as I ever could.
1 I put off making decisions more than I used to.
2 I have greater difficulty in making decisions than before.
3 I cannot make decisions at all anymore.

10. 0 I do not feel like I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance that make me look unattractive.
3 I believe that I look ugly.

11. 0 I can work about as well as before.
1 It takes an extra effort to get started at doing something.
2 I have to push myself very hard to do anything.
3 I cannot do any work at all.

12. 0 I do not get more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing almost anything.
3 I am too tired to do anything.

13. 0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all anymore.

Participant Number: _____

STAI

A number of statements which people have used to describe themselves are given below. Read each statement and then circle the appropriate number to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	Not at all applicable to me				Extremely applicable to me
I feel pleasant	1	2	3	4	5
I feel nervous and restless	1	2	3	4	5
I feel satisfied with myself	1	2	3	4	5
I wish I could be as happy as others seem to be	1	2	3	4	5
I feel like a failure	1	2	3	4	5
I feel rested	1	2	3	4	5
I am "calm, cool, and collected"	1	2	3	4	5
I feel that difficulties are piling up so that I cannot overcome them	1	2	3	4	5
I worry too much over something that really doesn't matter	1	2	3	4	5
I am happy	1	2	3	4	5
I have disturbing thoughts	1	2	3	4	5
I lack self-confidence	1	2	3	4	5
I feel secure	1	2	3	4	5
I make decisions easily	1	2	3	4	5
I feel inadequate	1	2	3	4	5
I am content	1	2	3	4	5
Some unimportant thought runs through my mind and bothers me	1	2	3	4	5

I take disappointments so keenly that I can't put them out of my mind	1 2 3 4 5
I am a steady person	1 2 3 4 5
I get in a state of tension or turmoil as I think over my recent concerns and interests	1 2 3 4 5

Participant Number: _____

Letter-Number span

Instructions

Make sure that the respondent can repeat the alphabet correctly. Then, state to the respondent: I am going to say a list of numbers and letters. When I am through, I want you to first tell me the numbers in order from smallest to biggest. Then I want you to tell me the letters in alphabetical order. So, for example, if I say A4, the answer is 4A. The number goes first, then the letter. If I say 8B2, you answer 28B, numbers first in order, then letters.

Discontinue

Discontinue after scores of 0 on *all four trials of an item section.*

Administration of Test

Administer all four items at each level until all items are failed at a level. Items should be read to the respondent at a rate of one letter or number per second. Instructions may be repeated in the beginning during the 2-symbol sequence when respondents are especially likely to misinterpret the instructions.

		RESPONSES		
Section	Item	Correct	Respondent's	Score
I.	D-6 4-L M-2 3 - B	6-D 4-L 2-M 3 - B		
IL	A-l-C W-7-T 5-R-8 9-X-3	1-A-C 7-T-W 5-8-R 3-9-X		
III.	Y-8-G-2 J-3-N-1 2-Z-5-H 4-F-5-S	2-8-G-Y 1-3-J-N 1-5-H-Z 4-5-F-S		
IV.	4-L-5-C-8 B-1-J-7-W 9-K-3-E-2 N-6-R-2-L	4-5-8-C-L 1-7-B-J-W 1-3-9-E-K 2-6-N-R-F		
V.	D-7-G-4-S-2 P-6-L-3-C-1 2-W-8-K-9-A 4-J-S-T-7-X	2-4-7-D-G-S 1-3-6-C-L-P 1-8-9-A-K-W 4-5-7-J-T-X		
VI.	C-7-G-4-Q-I-S 8-R-6-M-3-F-2 A-2-E-6-J-9-T 3-7-4-P-7-M-9	1-4-7-C-G-Q-S 3-6-8-F-M-R 2-6-9-A-E-J-T 3-4-7-9-M-P-T		

Participant number_____

A-S Q

Please read the following statements. To the right of each you will find four numbers, ranging from "1" (Definitely Disagree) on the left to "4" (Definitely agree) on the right. Circle the number which best indicates your feelings about that statement. For example, if you strongly disagree with a statement, circle "1" and if you strongly agree, circle "4", etc.

	Definitely disagree			Definitely agree
1. I prefer to do things with others rather than on my own	1	2	3	4
2. I prefer to do things the same way over and over again	1	2	3	4
3. If I try to imagine something I find it very easy to create a picture of it in my mind.	1	2	3	4
4. I frequently get so strongly absorbed in one thing that I lose sight of other things.	1	2	3	4
5. I often notice small sounds when others do not	1	2	3	4
6. I usually notice car number plates or similar strings of information.	1	2	3	4
7. Other people frequently tell me that what I've said is impolite, even though I think it is polite	1	2	3	4
8. When I'm reading a story, I can easily imagine what the characters might look like.	1	2	3	4
9. I am fascinated by dates.	1	2	3	4
10. In a social group, I can easily keep track of several different people's conversations.	1	2	3	4
11. I find social situations easy	1	2	3	4
12. I tend to notice details that others do not.	1	2	3	4
13. I would rather go to a library than a party.	1	2	3	4
14. I find making up stories easy.	1	2	3	4
15. I find myself drawn more strongly to people than to things	1	2	3	4
16. I tend to have very strong interests, which I get upset about if I can't pursue	1	2	3	4
17. I enjoy social chit-chat	1	2	3	4
18. When I talk, it isn't always easy for others to get a word in edgeways	1	2	3	4

19. I am fascinated by numbers.	1	2	3	4
20. When I'm reading a story, I find it difficult to work out the characters' intentions	1	2	3	4
21. I don't particularly enjoy reading fiction.	1	2	3	4
22. I find it hard to make new friends.	1	2	3	4
23. I notice patterns in things all the time	1	2	3	4
24. I would rather go to the theatre than a museum.	1	2	3	4
25. It does not upset me if my daily routine is disturbed	1	2	3	4
26. I frequently find that I don't know how to keep a conversation going	1	2	3	4
27. I find it easy to "read between the lines" when someone is talking to me	1	2	3	4
28. I usually concentrate more on the whole picture, rather than the small details	1	2	3	4
29. I am not very good at remembering phone numbers.	1	2	3	4
30. I don't usually notice small changes in a situation, or a person's appearance	1	2	3	4
31. I know how to tell if someone listening to me is getting bored	1	2	3	4
32. I find it easy to do more than one thing at once	1	2	3	4
33. When I talk on the phone, I'm not sure when it's my turn to speak	1	2	3	4
34. I enjoy doing things spontaneously	1	2	3	4
35. I am often the last to understand the point of a joke.	1	2	3	4
36. I find it easy to work out what someone is thinking or feeling just by looking at their face	1	2	3	4
37. If there is an interruption, I can switch back to what I was doing very quickly	1	2	3	4
38. I am good at social chit-chat	1	2	3	4
39. People often tell me that I keep going on and on about the same thing	1	2	3	4
40. When I was young, I used to enjoy playing games involving pretending with other children	1	2	3	4
41. I like to collect information about categories of things (e.g. types of car, types of bird, types of train, types of plants, etc.)	1	2	3	4
42. I find it difficult to imagine what it would be like to be someone else	1	2	3	4

43. I like to plan any activities I participate in carefully	1	2	3	4
44. I enjoy social occasions	1	2	3	4
45. I find it difficult to work out people's intentions	1	2	3	4
46. New situations make me anxious.	1	2	3	4
47. I enjoy meeting new people	1	2	3	4
48. I am a good diplomat.	1	2	3	4
49. I am not very good at remembering people's date of birth	1	2	3	4
50. I find it very easy to play games with children that involve pretending	1	2	3	4

Participant Number: _____

CDRISC Resilience Scale ™

Please read the following statements. To the right of each you will find seven numbers, ranging from "1" (Strongly Disagree) on the left to "7" (Strongly Agree) on the right. Circle the number which best indicates your feelings about that statement. For example, if you strongly disagree with a statement, circle "1". If you are neutral, circle "4", and if you strongly agree, circle "7", etc.

	Strongly Disagree						**Strongly Agree**
1. When I make plans, I follow through with them.	1	2	3	4	5	6	7
2. I usually manage one way or another.	1	2	3	4	5	6	7
3. I am able to depend on myself more than anyone else.	1	2	3	4	5	6	7
4. Keeping interested in things is important to me.	1	2	3	4	5	6	7
5. I can be on my own if I have to.	1	2	3	4	5	6	7
6. I feel proud that I have accomplished things in life.	1	2	3	4	5	6	7
7. I usually take things in stride.	1	2	3	4	5	6	7
8. I am friends with myself.	1	2	3	4	5	6	7
9. I feel that I can handle many things at a time.	1	2	3	4	5	6	7
10. I am determined.	1	2	3	4	5	6	7
11. I seldom wonder what the point of it all is.	1	2	3	4	5	6	7
12. I take things one day at a time.	1	2	3	4	5	6	7
13. I can get through difficult times because I've experienced difficulty before.	1	2	3	4	5	6	7
14. I have self-discipline.	1	2	3	4	5	6	7
15. I keep interested in things.	1	2	3	4	5	6	7
16. I can usually find something to laugh about.	1	2	3	4	5	6	7
17. My belief in myself gets me through hard times.	1	2	3	4	5	6	7
18. In an emergency, I'm someone people can generally rely on.	1	2	3	4	5	6	7
19. I can usually look at a situation in a number of ways.	1	2	3	4	5	6	7
20. Sometimes I make myself do things whether I want to or not.	1	2	3	4	5	6	7
21. My life has meaning.	1	2	3	4	5	6	7
22. I do not dwell on things that I can't do anything about.	1	2	3	4	5	6	7
23. When I'm in a difficult situation, I can usually find my way out of it.	1	2	3	4	5	6	7
24. I have enough energy to do what I have to do.	1	2	3	4	5	6	7

25. It's okay if there are people who don't like me.	1	2	3	4	5	6	7
26. I am resilient.	1	2	3	4	5	6	7

University of Roehampton London

PARTICIPANT DEBRIEF

Title of Research Project: Investigating cognitive processes during social interactions
Ethics reference N: PSYC 18/ 307

Thank you very much for taking part in our study, we greatly appreciate your contribution.

This study was designed to investigate how activity specific areas of the brain (e.g. the medial prefrontal cortex and amygdala) are activated during tasks tapping social cognition (tasks investigating how we learn from social cues around us). We were also interested in investigating the relationship between activities in these brain regions and a relation to different levels of personality traits. To do this we asked you to complete a series of simple tasks in the scanner and complete some questionnaires after the scan. During two of the tasks in this study you were again told that you are playing another player, i.e. an adviser, is giving you advice. The responses were pre-programmed into the task and you were not playing another person. We did not alert you to this component of the session as we wanted to investigate the nature of social interactions.

In some instances, we may be required to release your details to your GP (detailed in *"What are risks and benefits"* on the study consent form). Otherwise, all the information about your participation in this study will be kept strictly confidential. Your results will be coded with a participant number and no personal information will be attached to the data. This anonymisation will occur at the earliest point of data collection. Data will be stored on a University computer for 10 years, while personal details will be stored separately in a locked filing cabinet. Only the named researchers and responsible individuals from the University of Roehampton will have access to these data. The overall results of the study may be published in scientific journals. However, all personal data will remain confidential, and no data relating to individual participants will be published. Responsible members of the University of may be given access to data for monitoring and/or audit of the study to ensure we are complying with regulations. All will have a duty of confidentiality to you as a research participant.

Please note: if you have a concern about any aspect of your participation or any other queries please raise this with the investigator (or if the researcher is a student you can also contact the Director of Studies.) However, if you would like to contact an independent party please contact the Head of Department.

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Schizotypy Personality Questionnaire

Please indicate “yes” or “no” to each question.

1. Do you sometimes feel that things you see on the TV or read in the newspaper have a special meaning for you?

2. I sometimes avoid going to places where there will be many people because I will get anxious.

3. Have you had experiences with the supernatural?

4. Have you often mistaken objects or shadows for people, or noises for voices?

5. Other people see me as slightly eccentric (odd).

6. I have little interest in getting to know other people.

7. People sometimes find it heard to understand what I am saying.

8. People sometimes find me aloof and distant.

9. I am sure I am being talked about behind my back.

10. I am aware that people notice me when I go out for a meal or to see a film.

11. I get vey nervous when I have to make polite conversation.

12. Do you believe in telepathy (mind-reading)?

13. Have you ever had the sense that some person or force is around you even though you cannot see anyone?

14. People sometimes comment on my unusual mannerisms and habits.

15. I prefer to keep to myself.

16. I sometimes jump quickly from one topic to another when speaking.

17. I am not good at expressing my true feelings by the way I talk and look.

18. Do you often feel that other people have it in for you?

19. Do some people drop hints about you or say things with a double meaning?

20. Do you ever get nervous when someone is walking behind you?

21. Are you sometimes sure that other people can tell what you are thinking?

22. When you look at a person, or yourself in a mirror, have you ever seen the face change right before your eyes?

23. Sometimes other people think that I am a little strange.

24. I am mostly quiet when with other people.

25. I sometimes forget what I am trying to say.

26. I rarely laugh and smile.

27. Do you sometimes get concerned that friends or co-workers are not really loyal or trustworthy?

28. Have you ever noticed a common event or object that seemed to be a special sign for you?

29. I get anxious when meeting people for the first time.

30. Do you believe in clairvoyance (psychic forces, fortune telling)?

31. I often hear a voice speaking my thoughts aloud.

32. Some people think that I am a very bizarre person.

33. I find it hard to be emotionally close to other people.

34. I often ramble on too much when speaking.

35. My “nonverbal” communication (smilling and nodding during a conversation) is not very good.

36. I feel I have to be on my guard even with friends.

37. Do you sometimes see special meanings in advertisements, shop windows, or in the way things are arranged around you?

38. Do you often feel nervous when you are in a group of unfamiliar people?

39. Can other people feel your feelings when they are not there?

40. Have you ever seen things invisible to other people?

41. Do you feel that there is no one you are really close to outside of your immediate family, or people you can confide in or talk to about personal problems?

42. Some people find me a bit vague and elusive during a conversation.

43. I am poor at returning social courtesies and gestures.

44. Do you often pick up hidden threats or put-downs from what people say or do?

45. When shopping do you get the feeling that other people are taking notice of you?

46. I feel very uncomfortable in social situations involving unfamiliar people.

47. Have you had experiences with astrology, seeing the future, UFOs, ESP, or a sixth sense?

48. Do everyday things seem unusually large or small?

49. Writing letters to friends is more trouble than it is worth.

50. I sometimes use words in unusual ways.

51. I tend to avoid eye contact when conversing with others.

52. Have you found that it is best not to let other people know too much about you?

53. When you see people talking to each other, do you often wonder if they are talking to you?

54. I would feel very anxious if I had to give a speech in front of a large group of people.

55. Have you ever felt that you are communicating with another person telepathically (by mind-reading)?

56. Does your sense of smell sometimes become unusually strong?

57. I tend to keep in the background on social occasions.

58. Do you tend to wander off the topic when having a conversation?

59. I often feel that others have it in for me.

60. Do you sometimes feel that other people are watching you?

61. Do you ever suddenly feel distracted by distant sounds that you are not normally aware of?

62. I attach little importance to having close friends.

63. Do you sometimes feel that people are talking about you?

64. Are your thoughts sometimes so strong that you can almost hear them?

65. Do you often have to keep an eye out to stop people from taking advantage of you?

66. Do you feel that you cannot get “close” to people?

67. I am an odd, unusual person.

68. I do not have an expressive and lively way of speaking.

69. I find it hard to communicate clearly what I want to say to people.

70. I have some eccentric (odd) habits.

71. I feel very uneasy talking to people I do not know well.

72. People occasionally comment that my conversation is confusing.

73. I tend to keep my feelings to myself.

74. People sometimes stare at me because of my odd appearance.

Social Desirability Scale

Please indicate “true” or “false” to each comment.

1. It is sometimes hard for me to go on with my work if I am not encouraged.

2. I sometimes feel resentful when I don’t get my way.

3. On a few occasions, I have given up doing something because I thought too little of my ability.

4. There have been times when I felt like rebelling against people in authority even though I knew they were right.

5. No matter who I am talking to, I’m always a good listener.

6. There have been occasions when I took advantage of someone.

7. I am always willing to admit it when I make a mistake.

8. I sometimes try to get even rather than forgive and forget.

9. I am always courteous, even to people who are disagreeable.

10. I have never been irked when people expressed ideas very different from my own.

11. There have been times when I was quite jealous of the good fortune of others.

12. I am sometimes irritated by people who ask favours of me.

13. I have never deliberately said something that hurt someone’s feelings.