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INFORMATION PROCESSING AND EXPECTATIONS IN DELUSION-PRONENESS

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INFORMATION PROCESSING AND EXPECTATIONS IN DELUSION-PRONENESS

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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To my beloved Grandfather and Grandmother

ABSTRACT

One of the most characteristic features of psychosis is delusional ideation. Delusions represent incorrect and inflexible beliefs that are not based on reality. It has been proposed that delusions may be secondary to impairments in reality monitoring. These systems are formalised in a predictive coding framework, building on Bayesian inference theory, that describes the brain as an inference machine. In this framework, information processing is conceptualised as a multi-level pyramidal system that shows an increasing level of integration. The bottom levels (including primary sensory cortex) process simple sensory input while higher levels are associated with information processing of increasing complexity.

It has been suggested that in psychosis aberrant salience attribution leads to deficits in the lower levels of this hierarchical system, which in turn result in abnormal sensory experiences. Moreover, it has been proposed that delusions are formed in order to make sense of these unusual experiences that cannot be explained with normal logic.

Overly inflexible beliefs and delusions are not solely manifest in psychotic patients. They are also present, to a lesser degree, in the general population. For example, they are represented in a personality trait referred to as delusion-proneness. In the work presented in this thesis, we decided to study delusion-proneness in a healthy population in order to better understand the mechanisms underlying this trait.

Using different paradigms tackling self-recognition, decision making processes, and fear learning we confirmed that delusion-prone individuals show behavioural impairments similar (but attenuated) to psychotic patients. Taken together, our results bring support to the idea that delusion-proneness shows a double dissociation in the information processing hierarchy, with high-level prediction systems exerting an overly strong influence over imprecise lower-level prediction systems. While delusion-prone individuals show difficulties in generating low-level expectation signals, they tend to integrate more readily higher-order signals (i.e. beliefs) and overly rely on them in order to understand their environment.

Our work also points towards an involvement of frontal brain regions, more precisely lateral orbito-frontal cortex (lOfc), in the processing of high-order input in delusion-proneness. Specifically, we found a larger effect of instructions on fear learning in delusion-prone individuals than in controls, which was associated with a stronger connectivity between lOfc and brain regions involved in fear and pain processing.

Our results also suggest trait co-morbidities between delusion-proneness and sub-clinical symptoms of Attention Deficit and Hyperactivity Disorders (ADHD), as well as Autism Spectrum Disorders (ASD). This argues for a better assessment of these traits in studies focusing on psychosis-related states.

While the results presented in this thesis need to be replicated and investigated in a clinical population, our studies have helped advance the understanding the mechanisms underlying delusion-proneness.

LIST OF SCIENTIFIC PAPERS

I. When Passive Feels Active - Delusion-Proneness Alters Self-Recognition in the Moving Rubber Hand Illusion

II. Delusion-proneness displays comorbidity with traits of Autistic-Spectrum Disorders and ADHD

III. Increased choice blindness in delusion-proneness

IV. Beliefs matter - Enhanced explicit fear learning in delusion-proneness

CONTENTS

LIST OF ABBREVIATIONS

ADHD	Attention Deficit and Hyperactivity Disorder
AMPA-R	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors
AQ	Autism Quotient
ASD	Autism-Spectrum Disorder
ASRS	Adult ADHD Self-Report Scale
AVH	Auditory Verbal Hallucination
BADE	Bias Against Disconfirmatory Evidence
BOLD	Blood Oxygenation Level Dependent
cACC	caudal Anterior Cingulate Cortex
CBD	Cannabidiol
CFI	Comparative Fit Index
CS	Conditioned Stimulus
deoxyHb	Deoxyhaemoglobin
ERP	Event-Related Potential
fMRI	functional Magnetic Resonance Imaging
FWE	Family-Wise Error
GABA	Gamma Amino Butyric Acid
GLM	General Linear Model
GWAS	Genome-Wide Association Studies
iCS	instructed Conditioned Stimulus
lOfc	Lateral Orbito-frontal Cortex
MMN	Mismatch Negativity
MR signal	Magnetic Resonance signal
niCS	non-instructed Conditioned Stimulus
NMDA-R	N-methyl D-aspartate receptors
NRM	New Religious Movement
oxyHb	Oxyhaemoglobin
PCP	Phencyclidine
PDI	Peters' Delusion Inventory

PE	Prediction Error
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PLE	Psychosis-Like Experiences
PPI	Psychophysiological Interaction
PPIn	Prepulse Inhibition
RDK	Random Dot Kinetogram
RHI	Rubber Hand Illusion
RMSEA	Root Mean Square Error of Approximation
ROI	Region Of Interest
SCR	Skin Conductance Response
SNP	Single Nucleotide Polymorphisms
SPM	Statistical Parametric Mapping (software)
SVC	Small Volume Correction
THC	delta-9-tetrahydrocannabinoid
UCS	Unconditioned Stimulus
UHR	Ultra-High Risk
vmPFC	Ventro-medial Prefrontal Cortex

I – Introduction

1) Schizophrenia

a. Symptoms and evolution of the concept of schizophrenia

Schizophrenia is a complex, chronic neurodevelopmental psychotic disorder with a lifetime morbid risk approaching 1% worldwide (McGrath et al. 2008), and associated with devastating consequences for patients and their family. Although conditions and symptoms similar to psychosis have been reported since ancient times (Evans et al. 2003), it was not before the mid-19th century that psychotic symptoms were considered forming a disorder entity (for a more detailed review see Tandon et al. 2009). Based on longitudinal observations of a large number of clinical cases, Emil Kraepelin (1856 – 1926) noted that some patients were displaying similar patterns in terms of symptoms and illness evolution that would always lead to severe cognitive and behavioural impairments. He was the first to group these symptoms previously considered as separate, into one single nosological entity he named *Dementia Praecox* (Kraepelin 1913).

Group of catatonic patients, from the fifth edition of Emil Kraepelin's Psychiatrie (Leipzig Johann Ambrosius Barth, 1896).

Eugen Bleuler (1857 – 1939) refined the description of the disorder, coining the term *schizophrenia* in order to replace *Dementia Praecox* (Jablensky 2010). While Kraepelin supported the concept of a unique disease entity, Bleuler stressed the fact schizophrenia was not a disease *sensu stricto*, but should rather be viewed as a group of diseases, due to the large spectrum of symptoms that could be found in those patients (Jablensky 2010). Bleuler also made a distinction between what he referred to as basic symptoms, used for diagnostic purposes, and accessory symptoms whose presence though frequently reported in these patients was not sufficient to give schizophrenia its characteristic diagnostic profile (Jablensky 2010). The concept of having some symptoms fundamental to the diagnosis of the disease, while others are accessory, influenced the way schizophrenia was described the DSM-4 (Pagsberg 2013).

In terms of symptomatology, psychosis is characterised by negative symptoms, positive symptoms and disorganisation symptoms (Liddle 1987; Cuesta & Peralta 1995). Negative symptoms refer to deficits in mental functions, including social withdrawal, poverty of speech, apathy, anhedonia, catatonia (Cuesta & Peralta 1995). Positive symptoms, on the other hand are florid manifestations, such as delusions (including paranoia) and hallucinations, that reflect aberrant mental activity (Kay et al. 1989; Liddle 1987; Cuesta & Peralta 1995). Disorganisation symptoms correspond to a fragmentation of normal logical thought process which manifests in speech impairments of varying degrees of severity, including incoherence, neologisms, derailment, loosening of associations (Covington et al. 2005; Andreasen 1979; Tandon et al. 2009). These impairments also translate into the behavioural domain with for instance social disinhibition, difficulty in goal-directed behaviours (Tandon et al. 2009). More general disturbances are also observed in executive functions (Heinrichs & Zakzanis 1998), working memory (Aleman et al. 1999; Silver et al. 2003; Forbes et al. 2009), and attention deficit (Cornblatt & Keilp 1994; Sullivan et al. 1994; Silverstein et al. 2003), which often result in dysfunctions in social adaptation and communication. Psychosis is not a mental disorder *per se*, but an ensemble of symptoms. Schizophrenia is a psychiatric disorder that corresponds to a type of psychosis, in which a person must present signs of disturbance for at least six months, with psychotic symptoms for at least one month, leading to a significant decline in her/his ability to function (Pagsberg 2013). Moreover, a psychotic episode can be observed during a short period and in isolation without any reoccurrence, and can also be part of a bipolar or depressive

disorder. In addition, various specific neurological disorders can be associated with psychotic symptoms. Finally, many drugs are associated with psychotic symptoms.

There is a substantial comorbidity between schizophrenia and other psychiatric disorders. For example, research is increasingly shedding light on symptom overlaps between schizophrenia and autism spectrum disorders (ASD) (Stahlberg et al. 2004; Chisholm et al. 2015) or attention deficit and hyperactivity disorders (ADHD) (Pallanti & Salerno 2015; Stahlberg et al. 2004; Larsson et al. 2013). The concept of schizophrenia as a unique disorder with supposedly specific criteria as described in the DSM, gets even more questioned when considering that about 5% of ADHD patients and 8% of individuals with ASD are also meeting criteria for schizophrenia or another psychotic disorder (Stahlberg et al. 2004).

The illness time course of schizophrenia shows four distinct phases; a premorbid phase, a prodromal phase, a psychotic phase, and a stable phase (Figure 1). Each of them shows various degrees of recovery. Interestingly, unlike other neurodevelopmental disorders like ADHD or ASD in which the impairments start to be apparent in early childhood, the first full-blown psychotic episode rarely occurs before late adolescence or early adulthood. Nevertheless, impairments are already present years before this phase.

Childhood is viewed as a premorbid phase (childhood onset schizophrenia is rare (Driver et al. 2013)) during which some subtle cognitive, motor, emotion, intellectual and behavioural impairments are already often apparent - while no manifest psychotic episode has occurred yet (Davidson 2001; Bilder et al. 2006; Woodberry et al. 2008; Schenkel & Silverstein 2004). However since the symptoms often remain limited and non-specific they are usually unnoticed although it has been suggested that psychotic symptoms occur in children and relate to development of schizophreniform disorder in adult age (Poulton et al. 2000). Although studies are now trying to identify markers in early phases, those subtle and imprecise impairments are often revealed in retrospect, after the first psychotic episode. The premorbid phase is followed by a prodromal period that takes place right before the first psychotic episode, and can span from a few weeks, up to a few years before the onset. In this phase, the cognitive, motor and behavioural deteriorations are more dramatic than in the premorbid phase (Ang & Tan 2004; Nørgaard et al. 2016; Tandon et al. 2009). Sleep disturbances are often observed,

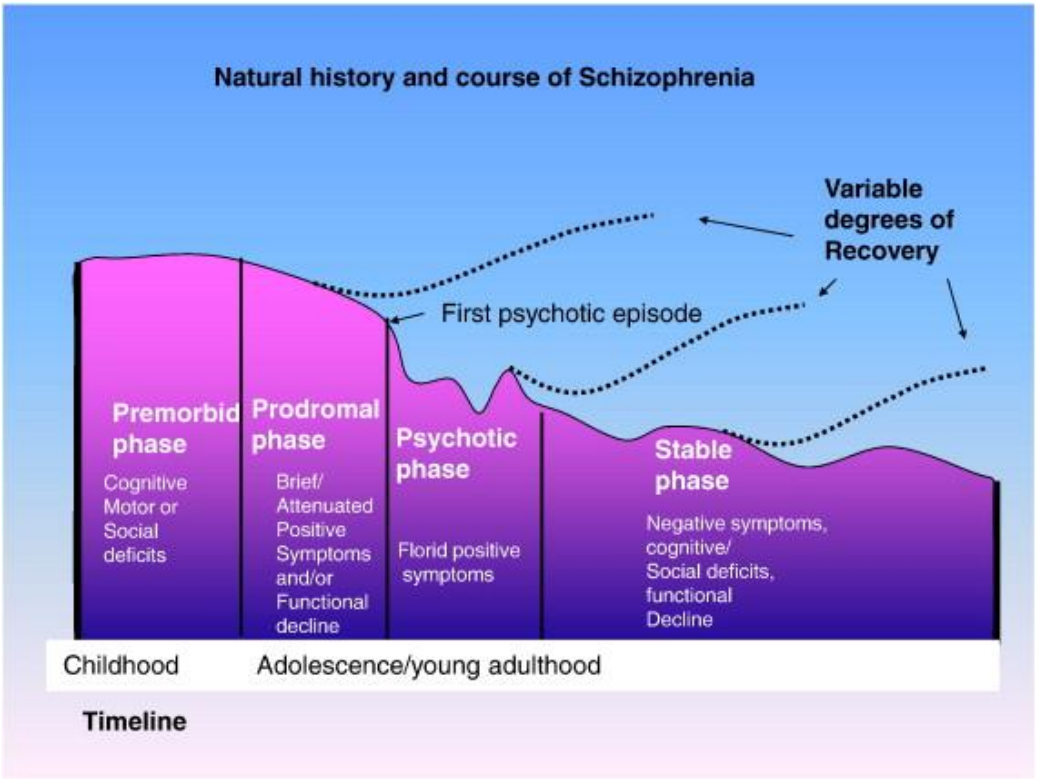

Figure 1. Evolution of schizophrenia with phases of illness. Reprinted from *Schizophrenia, "just the facts" 4. Clinical features and conceptualization*, Tandon, R., Nasrallah, H. A., & Keshavan, M. S., 1-23, Copyright 2009, with permission from Elsevier.

as well as perceptual abnormalities, concentration, language and memory impairments (Lencz et al. 2006; Fusar-Poli et al. 2012; Lee et al. 2015). Individuals may display negative symptoms first (i.e. social withdrawal, depression or anxiety), then transient positive psychotic symptoms start to appear. Strong, but imprecise, experiences of the world being different than before are common (Kapur 2003). The frequency and intensity of these symptoms increase with time until they reach pre-psychosis or subthreshold levels (e.g. pre-delusional thought disturbances, pre-hallucinatory perceptual abnormalities) (Larson et al. 2010; Yung & McGorry 1996). Although the definition of subthreshold symptoms is arbitrary, these symptoms differ from frank psychotic symptoms in terms of severity as well as duration, and importantly, they do not require antipsychotic medication (Yung et al. 2005; Larson et al. 2010). While partial or complete remission can occur at any stage, even when showing pre-psychotic symptoms (Schultze-Lutter 2009; Tandon et al. 2009), the individual may also fall into a full-blown psychotic phase, characterised by florid positive symptoms. The first psychotic episode is usually the moment when patients seek medical help and get a diagnosis. Psychotic phases vary in terms of duration and are usually followed by a

stable period during which positive symptoms attenuate, negative symptoms prevail, and functional deteriorations stabilise. While some individuals might only experience one psychotic episode, psychotic phases often reappear, and the duration of stable phases between two psychotic episodes varies greatly (Tandon et al. 2009).

b. Public health

Patients with schizophrenia need lifelong treatment, and it is frequent to have them admitted to hospital inpatient units on several occasions throughout their life. This leads to large direct costs in terms of expenditures for hospital and nursing home care, community support physicians, drug treatments and appliances. Costs related to lost productivity due to morbidity and premature mortality (indirect costs) also have to enter the picture. Schizophrenia symptoms are highly disabling, leading to poor social functioning and low employment rates (estimated to 10-20% in European countries (Marwaha & Johnson 2004)). This represents not only a productivity loss for the patients themselves but also for their care-givers who support them with their time and different services (Knapp et al. 2004). The resulting total costs for society are therefore highly significant. Based on data from 2008, the total annual cost per patient in Sweden was estimated to SEK 509,000 (EUR 55,100), with indirect costs accounting for up to 60% of this total cost (Ekman et al. 2014). Although hard to quantify in monetary terms, intangible costs describing the drawbacks of an illness such as pain or depression, should also be taken into consideration as they greatly influence indirect costs. Mortality is increased by almost 4-fold in those patients, and when looking at suicide risk in these patients, it is 8.5-fold greater than in the general population (Harris & Barraclough 1997). About a third of schizophrenia patients attempt suicide at least once, and 5% of patients die of suicide (Tandon et al. 2009). This risk is actually more than 3 times higher at the very beginning of the illness, than at any other time point (Palmer et al. 2005; Melle et al. 2006), hence the need to stress the importance of directing intervention and prevention efforts towards the early stages of the illness.

c. Other psychosis-related disorders

Although psychosis is a core feature of schizophrenia, it is important to bear in mind that it is also part of the symptomatology of other disorders. Psychosis can sometimes

manifest itself as a simple delusional disorder, whereby delusional ideation is present without any hallucination (Munro 1999). This is the case for instance in paranoia (Kendler 1980), delusion of parasitosis whereby patients are convinced their skin is infected by insects (Koo & Gambla 1996; Wilson & Miller 1946), or delusion of jealousy (also known as Othello syndrome) (Kingham & Gordon 2004; Leong et al. 1994). As mentioned previously, psychotic symptoms are also frequently reported in bipolar disorder and schizoaffective disorder. Bipolar disorders (or manic-depressive illness) correspond to a range of brain disorders causing unusual shifts in mood and energy levels, resulting in reduced ability to perform daily tasks (Akiskal & Pinto 1999; Hirschfeld et al. 2000). Bipolar disorder type 1 is in fact highly related to schizophrenia, genetically (Cardno & Owen 2014; Purcell et al. 2009). Psychosis is also frequently observed when these patients go through mood episodes (Pope & Lipinski 1978; Keck et al. 2003; Stahlberg et al. 2004). Patients presenting a schizoaffective disorder experience a combination of mood symptoms (depression, mania, etc) and schizophrenia-like symptoms including hallucinations, delusions, though disorders that are not always co-occurring (Pope et al. 1980). Finally, some organic (neurological) conditions can also lead to psychotic episodes. They range from neurodegenerative disorders (e.g. Alzheimer's disease, Parkinson's disease, Frontotemporal dementia) to epilepsy, cerebrovascular disease and vascular dementia, multiple sclerosis, brain tumour, or head injury (Lautenschlager & Förstl 2001). Although these conditions have different origins, they all involve some brain atrophy (either at the cortical level or in the limbic system) or imbalance between different neurotransmitter systems (Lautenschlager & Förstl 2001; Cummings 1988; Cummings 1992).

d. The concept of psychosis continuum

Despite the fact the notion of prodromal signs in psychosis was already present in Bleuler's work (Jablensky 2010), it was not before the 1960s that researchers started to move from a dichotomous conceptualisation of schizophrenia with symptoms being either present or absent, to a continuous perspective. Epidemiological and family studies began to reveal that psychotic symptoms were observed with different levels of severity in patients, and they could also be present at subclinical levels in the general population, in particular in patients' first-degree relatives (McConaghy 1959; Phillips et al. 1965; Chapman 1966; Kendler et al. 1993; Kendler et al. 1995). The concept of

schizotypy - a personality type presenting with some attenuated features of schizophrenia - emerged in the early 1960s (Jablensky 2010; Meehl 1962) and schizophrenia got increasingly viewed as "a point on a continuum" (Strauss JS 1969). In line with the idea of a prodrome, the dimensional distribution of subclinical symptoms has been shown to be linked to a vulnerability to develop a full-blown psychotic disorder (Linscott & van Os 2010; Dominguez et al. 2011; Meehl 1989). Due to schizophrenia heritability and the presence of subclinical symptoms in the general population, the concept of endophenotypes (i.e. stable phenotypes or trait associated with a presumed inherited vulnerability, usually identified in a laboratory rather than clinical setting (Gottesman & Gould 2003; Braff et al. 2007)) became increasingly relevant. The growing interest in finding reliable schizophrenia endophenotypes comes from the fact they may help elucidate pathophysiologic mechanisms behind the disorder, lead to new treatment development, and may allow early detection (Thaker 2007; Braff et al. 2007; Allen et al. 2009). However, it is important to stress that the presented dimensionality idea does not equal a continuum of psychotic symptoms from healthy subjects to patients. Instead, it mirrors how different individuals experience the world and relates to the risk of developing a clinical psychotic disorder (van Os et al. 2009). Many individuals with subclinical psychotic symptoms maintain a good function in life, and will never develop a clinical disorder. It has been suggested that the dimensionality of subclinical symptoms is related to specific information processing capacities of the individual (i.e. cognitive core capacity (Petrovic & Castellanos 2016). The vulnerability associated with the presence of such subclinical symptoms renders the study of psychosis-proneness highly relevant. The benefits are two-fold as this allows a better understanding of the mechanisms that lead to the transition from non-clinical levels to psychosis, and also to develop early intervention to prevent this transitioning or to limit the extent of negative outcome. It should be noted that the categorical approach should not be disregarded as it has practical advantages; it facilitates decision-making processes regarding diagnosis and communication among clinicians or researchers (Esterberg & Compton 2009). It is also easier to study treatment efficacy using a categorical approach (Esterberg & Compton 2009). However, one should keep in mind that while a categorical approach may be practical, a dimensional approach may be more appropriate when trying to understand mechanisms involved in schizophrenia.

e. Psychosis-proneness and delusion-proneness

As mentioned above, many core symptoms observed in psychotic disorders can also be reported to a lesser degree in healthy individuals. This proneness to psychosis-related symptoms is referred to as psychosis-proneness. The cognitive, thought- and perceptual mechanisms underlying psychosis-proneness are considered to be similar to the one underlying psychosis (Peters et al. 2004; van Os et al. 2009; Teufel et al. 2010; Fusar-Poli et al. 2013). Although psychosis-prone individuals have a greater risk to develop a frank psychosis, it should be stressed most of them will never develop a clinical significant psychotic disorder that includes loss of function (van Os et al. 2009; Kaymaz et al. 2012). It should be noted that psychosis-proneness should not be viewed as a trait that only bears deleterious aspects. It has been shown to be associated with creativity, which might represent an evolutionary advantage (Kyaga et al. 2011; Kyaga et al. 2013). Delusion-prone individuals represent an interesting study population as they are otherwise healthy and thus free from antipsychotic medications. They do not have co-morbidities, and their brain does not present chronic effect related to schizophrenia (e.g. cognitive decline). In addition, studying delusion-prone individuals might also help understand why certain individuals transition to full-blown psychosis, while other never go over that border.

Psychosis-proneness is often studied in terms of delusion-proneness. Delusions are defined as erroneous idiosyncratic beliefs (high-level priors), which are not based on reality and usually related to misunderstanding or misinterpretation of perceptual experiences (Coltheart et al. 2011; Fletcher & Frith 2009). They are characterised by a fixed, inflexible nature and patients' inability to reject implausible beliefs even in the face of contradictory evidence (Eisenacher & Zink 2016; Woodward et al. 2008). Delusion-proneness is a personality trait describing how prone people are to delusional ideation, and that shows a semi-normal distribution in the general population (Peters, Joseph, et al. 1999). By definition, delusion-proneness does not necessarily include hallucinations.

It should be stressed that delusion-prone individuals are to be differentiated from ultra-high risk (UHR) individuals. While delusion-proneness represents a trait associated with tendencies to psychosis-like experiences, people considered as at ultra-high risk

are individuals seeking medical help and showing prodromal signs of schizophrenia (Fusar-Poli et al. 2013). The transition rate to frank psychosis for UHR individuals is estimated to about 36% in a follow-up period of 3 years (Fusar-Poli et al. 2013). The reason why UHR individuals seek medical help in the first place is often related to other psychiatric problems like depression, anxiety disorders (Fusar-Poli et al. 2013). An important distinction between delusion-prone subjects and UHR is the experienced distress caused by the symptoms (Fusar-Poli et al. 2013).

f. Origins

1. Genetic causes

The neurodevelopmental hypothesis posits that schizophrenia is the result of a process spanning over the whole brain development period, and affecting some critical brain circuits. Abnormalities can occur as early as late first or second trimester in utero via maternal infections (e.g. influenza virus), although the exact mechanisms involved remain unclear (Fatemi 2005; Kneeland & Fatemi 2013; Brown 2011; Boksa 2008; Brown & Derkits 2010; Jakob & Beckmann 1986). Combined with other factors, these early abnormalities may result in the activation of some pathological neural circuits. The full-blown consequences appear once the brain reaches its mature state, in late adolescence/early adulthood (Fatemi & Folsom 2009).

The question of gender differences in schizophrenia is difficult to address as studies report conflicting evidence. The only well-documented gender difference is the age of onset. Several studies have reported that men usually develop the illness earlier (mean age of the onset 18–25) than women (age of onset 25–35) (Ochoa et al. 2012) (Figure 2). Several studies have supported the idea of an increased risk for male individuals (Aleman et al. 2003; McGrath et al. 2008; Iacono & Beiser 1992; Ochoa et al. 2012). Nevertheless, in terms of prevalence the question of gender is still being debated, due to the fact some of the results might be due to some methodological shortcomings rather than true differences (Häfner 2005).

There is a number of interrelated causes (genetic, neurobiological and environmental) underlying schizophrenia spectrum disorders with many stemming back to prenatal development as mentioned above. Grey and white matter reductions have been

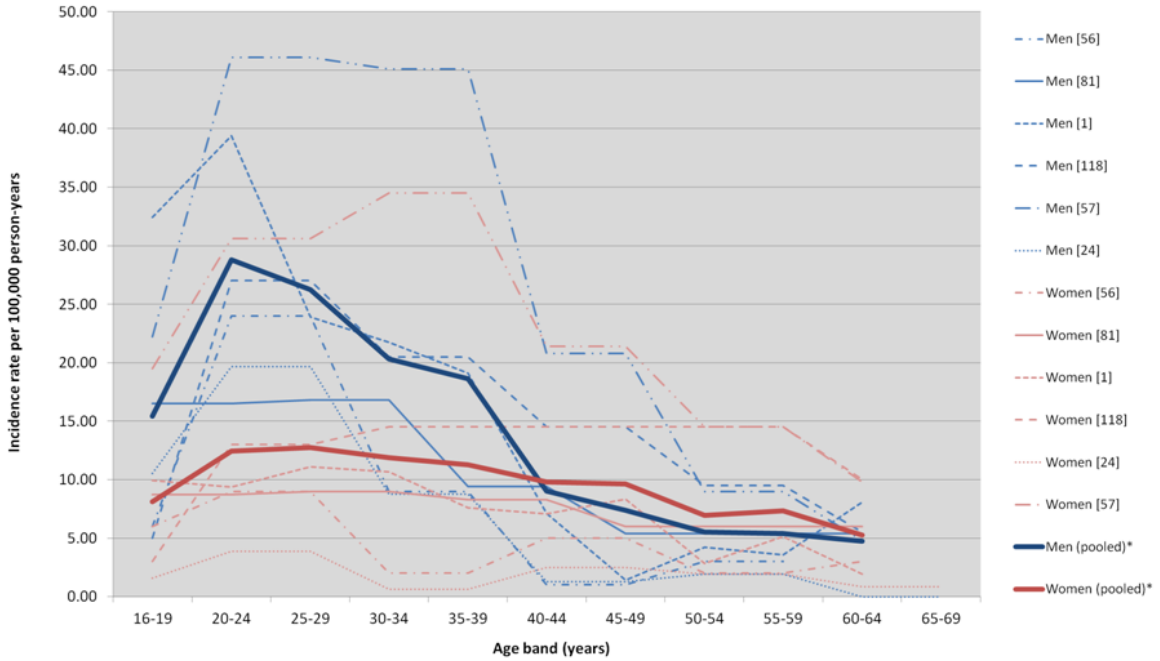

Figure 2. Incidence of schizophrenia by age and gender in England, 1950-2009, pooled and per relevant citation. The thin solid and dashed lines present rates of schizophrenia from individual studies for men and women, respectively. Thick solid lines present the unweighted mean rate for each strata, from these studies. Unweighted means are preferred in this instance because no model assumption underpins the data. – Reprinted from *Incidence of Schizophrenia and Other Psychoses in England, 1950–2009: A Systematic Review and Meta-Analyses.* Kirkbride, et al. PLOS ONE. 2012. 7(3)

consistently reported in various frontal, temporal and limbic areas in schizophrenia patients (Bogerts et al. 1985; Bora et al. 2011; Sigmundsson et al. 2001). Post-mortem studies have revealed that the grey matter reduction observed in schizophrenia is related to morphological changes in pyramidal neurons rather than neuronal loss. It was reported that the soma of pyramidal cells in layer 3 of the dorsolateral prefrontal cortex, primary and associative auditory cortices was 10% smaller in schizophrenia patients (Glausier & Lewis 2013). Shorter dendrites and a lower density of dendritic spines are also thought to contribute to the decreased neuropil observed in schizophrenia (Jaaro-Peled et al. 2010; Glausier & Lewis 2013; Iritani 2013). In addition, the vast majority of excitatory synapses in the central nervous systems are located on dendritic spines. Thus the decrease in these spines may also explain some of the neurotransmitter imbalance reported in schizophrenia (Glausier & Lewis 2013). Changes in oligodendrocytes and interneurons in terms of cell numbers and gene expression have also been reported (Jaaro-Peled et al. 2010). However despite these different observations neurobiological causes and molecular mechanisms of schizophrenia still remain largely incomplete (Gejman et al. 2010). The fact

schizophrenia presents a complex symptomatology, with patients displaying a variety of symptoms, makes the identification of causal genes even more challenging. The large interest in genetic factors involved in schizophrenia originated from findings related to heritability, showing that the risk for developing schizophrenia is higher if a first-degree relative has the condition. Children born from two parents with schizophrenia have an estimated 46% greater risk for developing the disorder themselves, as compared to the 1% lifetime risk in the general population (Combs et al. 2012). Genome-wide association studies (GWAS) have been developed in order to identify genetic factors involved in the risk of developing schizophrenia. GWAS aim to identify in a very large population, genome-wide single nucleotide polymorphisms (SNPs) associated with a trait or a disorder, and often summarise the variation in multiple genetic loci and their associated weights using a number called polygenic score (Dudbridge 2013; de Vlaming & Groenen 2015). So far, the different studies looking at polygenic risk profiles for schizophrenia have reported many common variants of very small effect when viewed individually, but that collectively form a substantial polygenic component of schizophrenia risk when considered collectively (Purcell et al. 2009; Henriksen et al. 2017). The cumulative effect was found to account up to a third of the total variation in liability (Purcell et al. 2009; Henriksen et al. 2017; Lee et al. 2012; Ripke et al. 2013). Today, the limited value of these scores in terms of individual risk prediction prevents a clinical application, as diagnostic tools or clinical genetic testing for schizophrenia. However, in the future, more refined polygenic scores might prove useful in order to assess the risk of schizophrenia in individuals.

Thus, despite family or twin studies reporting high heritability estimates (Gejman et al. 2010; Sullivan et al. 2003; Kety 1987), researchers have failed to univocally demonstrate genetic factors are the sole origin of schizophrenia. Monozygotic twins are genetically identical, while dizygotic twins, siblings, and parents share approximately 50% of their genes. If a phenotype is determined entirely by genetic factors, monozygotic twins should show a concordance of 100%, while other first-degree relatives (dizygotic twins, siblings, parents) should show a concordance about 50% (Tsuang 2000). Existing twin studies have reported concordance rates of schizophrenia for monozygotic twins to only approach 40%-50%, thus suggesting genetic factors do not fully account for schizophrenia (Tsuang 2000; Insel 2010; Cardno & Owen 2014; Gejman et al. 2010). In addition, it should be noted that these figures are slightly

overestimated due to some study limitations and the general failure to clearly isolate the influence of genetic factors from environmental ones (Kringlen 2000; Gottesman & Shields 1976).

2. Environmental and epigenetic causes

Epigenetic changes are induced by the environment in the parents and then transmitted to the individual that will develop the disorder (and often relate to what genes are expressed and how much they are expressed by various methods such as DNA-methylation) while environmental changes may directly affect the individual at risk (Skinner et al. 2010; Dolinoy et al. 2007). There is a growing body of evidence for the role of environmental and epigenetic factors in schizophrenia, showing that individual-specific environmental effects explain almost 20% of the variance in liability to schizophrenia (Cardno & Gottesman 2000; Brown 2011). The ones that have been reported the most frequently include various obstetric complications, famines, migrant status, seasonal effects (via prenatal infections) and living in an urban area (Gejman et al. 2010).

2.1 Urbanicity

It has consistently been reported that growing up in urban areas is associated with the risk to develop schizophrenia or psychotic disorders (Krabbendam & Van Os 2005; Vassos et al. 2012). The idea of a link between an urban environment and schizophrenia was first introduced in the late 1930s by Faris and Dunham, who found a much larger rate of incidence of schizophrenia (about 6 folds) in the centre of Chicago than in its outskirts (Faris & Dunham 1939). The communities living in the inner areas of the city were described as more disorganized and unstable, with social isolation and poor communication among residents. Although these results were preliminary and possibly subjected to several limitations, they sparked some interest in that direction, leading to more studies that confirmed those observations. Almost half a century later, Lewis *et al* reported the incidence of schizophrenia was almost 50% higher for men who had had an urban upbringing than for those who had been brought up in rural areas (Lewis et al. 1992). Using a large cohort (everyone born in Denmark with a known maternal identity, between January 1956 and December 1983, and alive by their 15th birthday; n=1.89 million people), Pedersen and colleagues found a dose-response relation

between urbanicity during upbringing and schizophrenia risk (Pedersen & Mortensen 2001). Marcelis and colleagues reported that a continuous or repeated urbanicity exposure during childhood and adolescence, rather than around or after the onset of psychosis, had a risk-increasing effect on psychosis-proneness. In addition, in case of subclinical psychosis features in adolescence, growing up in an urban environment seems to worsen the outcome consequences of the developmental expression of psychosis (Spauwen et al. 2006). The fact urban exposure rather seems to matter during upbringing rather than adulthood, also supports the developmental origin of the mechanisms involved schizophrenia (Marcelis et al. 1999). However, it should be kept in mind that most of the factors linking urbanicity to this increased risk of developing schizophrenia remain largely undetermined and hypothetical. Importantly, casual relations between urbanicity and development of schizophrenia have not been established. Some studies suggest the role of urbanicity *per se* might have been overemphasised, and propose that familial may explain most of the differences of schizophrenia prevalence observed between urban and non-urban environments (Sariaslan et al. 2015; Sariaslan et al. 2016).

2.2 Social isolation

High deprivation and social isolation in the wider social environment (i.e. neighbourhood – social network is reported as poorer in cities than in rural areas) have been reported as key risk factors (Sundquist et al. 2004). More specifically, social capital, defined as "the features of social organisation, such as civic participation, norms of reciprocity, and trust in others, that facilitate cooperation for mutual benefit" (Kawachi et al. 1997), is increasingly considered as central in the incidence and prevalence of mental illness, including neurosis and schizophrenia (McKenzie et al. 2002; Kawachi et al. 1997). Low-levels of cognitive social capital, mutual trust, bonding, safety in neighbourhoods, increased loneliness (Lamster, Lincoln, et al. 2017), discrimination and perception of personal injustice (Padhy et al. 2014; Wickham & Bentall 2016) are believed to impact dramatically on developmental mechanisms, resulting in enhanced emergence of *at-risk* mental states that may eventually facilitate the onset of clinical psychosis in adulthood (Kawachi et al. 1997; Krabbendam & Van Os 2005). A reduction in loneliness in delusion-prone individuals has actually been associated with a reduction in paranoid beliefs (Lamster, Nittel, et al. 2017). Loneliness and social exclusion may even have a causal relation to paranoia. Indeed, when

combined with cognitive impairment, as observed in schizophrenia, they may lead to increased negative and wrong schemata of others, which can easily result in paranoid beliefs (Lamster, Lincoln, et al. 2017; Westermann et al. 2012). Patients facing social isolation have no other feedback on their experiences than their own distorted beliefs. This might play a role in the maintenance of abnormal reasoning (Garety et al. 2001). In addition, although a stable and supportive social surrounding might not reduce the occurrence of anomalous experiences in patients, it might still help alleviate part of the distress and anxiety associated with these events, resulting in better outcome. This is supported by studies showing that distress associated with psychosis-like experiences (PLE) is a key element when differentiating clinical populations from at-risk populations (mainly new religious movement – NRM – populations) (Peters, Day, et al. 1999; Lim et al. 2011). Indeed, while individuals from NMR or paranormal believers report levels of PLE similar to psychotic patients, they are significantly less distressed by those experiences than patients (Peters, Day, et al. 1999; Lim et al. 2011; Lim et al. 2014; Cella et al. 2012). This observation makes sense when one considers the fact psychotic patients only receive a diagnosis when they go to a psychiatry ward. It is reasonable to think that distress is one of the main factors that would lead someone to seek medical help. If PLE or delusions are not particularly distressing, they might have a more limited impact on functioning abilities of the person experiencing them. Thus, the individual displaying psychotic symptoms might never get a diagnosis. The influence of distress on psychosis diagnosis can thus partly explain the protective role of social support (Lim et al. 2014; Hultman et al. 1997; Kuipers et al. 2006; Garety et al. 2001).

2.3 Drug consumption

The frequent intake of drugs of abuse also represents a substantial factors in gene-environmental interactions in the context of psychosis (Radhakrishnan et al. 2014; Nielsen et al. 2017; Henquet et al. 2008; Henquet et al. 2005). Although the exact mechanisms explaining this effect are still unclear, the general idea postulates that a regular cannabis consumption is associated with a greater risk to a full-blown psychotic episode (Andréasson et al. 1987; Zammit et al. 2002; Linszen 1994; Henquet et al. 2005; Henquet et al. 2008; Radhakrishnan et al. 2014), probably via dopamine sensitisation (McDonald & Murray 2000; Radhakrishnan et al. 2014). It is thought that most of cannabis psychoactive effects come from delta-9-tetrahydrocannabinoid (THC)

(Radhakrishnan et al. 2014; McDonald & Murray 2000). However, cannabis also contains cannabidiol (CBD), a cannabinoid that has been shown to have antipsychotic properties (Radhakrishnan et al. 2014). Thus, cannabinoid composition of cannabis plays a role in its psychotropic effects. However it should be stressed that cannabis is neither a necessary nor a sufficient cause of psychosis (Kuepper et al. 2010; McDonald & Murray 2000). Therefore, it cannot be described as a purely biological cause.

While cannabis consumption appears to be the highest risk factor in terms of drugs of abuse, cocaine and amphetamine can also lead to psychosis (Nielsen et al. 2017). However, drug-induced psychoses should not be confused with schizophrenia, as they do not usually lead to a diagnosis (Bramness et al. 2012). Nevertheless, repeated exposure to cocaine or amphetamine (and to a lesser extent alcohol) increases vulnerability (Thirthalli & Benegal 2006; Bramness et al. 2012), and their consumption by patients worsens psychotic symptoms and renders treatment more difficult (Dermatis et al. 1998; Winklbaur et al. 2006).

g. Pathophysiological mechanisms

Identifying the exact pathophysiological mechanisms of psychosis is not an easy task. Although several systems and related processes have been suggested to be involved in the development of psychosis, findings are still unclear. The dopamine hypothesis is probably one of the oldest and most investigated theories. Considering the critical role dopamine plays in salience attribution, the well-documented salience dysfunctions in schizophrenia (Kapur 2003) support the idea of dopamine as a key neuromodulator in schizophrenia.

1. The role of dopamine

Three lines of evidence suggest the involvement of the dopamine system in psychosis and schizophrenia. First, researchers' interest in the role of dopamine in psychosis originates from the discovery that antipsychotic drugs were acting as dopamine receptor antagonists (Carlsson et al. 1957; Carlsson & Lindqvist 1963). Secondly, it has been shown that administration of psychostimulants that induce dopamine release, such as amphetamine, leads to an exacerbation of psychotic symptoms in schizophrenia

patients (Laruelle et al. 1996), and induces psychotic-like symptoms in healthy individuals (Lieberman et al. 1987). More specifically, it is thought that by inducing an increase in phasic dopamine firing in the striatum, psychostimulants render striatal dopamine transients aberrant and unable to selectively signal relevant stimuli, which disrupts the adaptive behavioural response and thus mimics psychotic symptoms or worsens existing ones (Maia & Frank 2017; Dela Peña et al. 2015; Wanat et al. 2009). Finally, amphetamine-induced dopamine release positron emission tomography (PET) studies suggest that schizophrenia patients (Laruelle et al. 1996; Abi-Dargham et al. 1998; Breier et al. 1997; Abi-Dargham et al. 2004; Weinstein et al. 2017) and psychosis-prone individuals (Howes et al. 2009; Fusar-Poli et al. 2011; Egerton et al. 2013; Woodward et al. 2011) show a more sensitive dopamine system with a heightened level of synaptic dopamine. In addition, studies assessing dopamine synthesis by measuring the reuptake of a radioactive dopamine precursor analogue (l-[β-11C]DOPA (11C-DOPA) or 6-[18F]fluoro-L-DOPA (18F-DOPA)) in presynaptic monoaminergic neurons, revealed that dopamine synthesis was elevated in schizophrenia patients (Lindström et al. 1999; McGowan et al. 2004), first-degree relatives (Huttunen et al. 2008), and at-risk individuals (Howes et al. 2009). However, striatal receptor levels has not reliably show to be different in unmediated patients versus controls (Howes et al. 2012).

A more refined picture of the role of dopamine in psychosis appeared when studies identified the separate effects of D_1 (predominantly cortical distribution) and D_2 receptors (predominantly subcortical/striatal distribution) in psychosis (Davis et al. 1991). These studies suggested that schizophrenia was associated with a reduced D_1 transmission in frontal areas, while striatal D_2 transmission was increased. Moreover, prefrontal dopamine release has shown to be attenuated in patients (Slifstein et al. 2015). Due to these receptors specific distribution, this led to the development of the concept of fronto-striatal dysfunction. The two dopaminergic systems are closely connected (Meyer-Lindenberg et al. 2002), and interact in a bidirectional fashion. It has been suggested that the prefrontal hypodopaminergia results in an increase in striatal dopamine (Howes & Kapur 2009), while at the same time, subcortical hyperdopaminergia inhibits prefrontal function in schizophrenia (Kegeles et al. 2010) and to some extent in at-risk individuals (Fusar-Poli et al. 2011). It has been hypothesised that frontal dopaminergic dysfunction (hypodopaminergia) underlie negative and cognitive symptoms (Goldman-Rakic et al. 2004; Slifstein et al. 2015),

while conversely, positive symptoms may to a larger extent originate from striatal hyperdopaminergia (Davis et al. 1991; Howes & Kapur 2009; Van Der Gaag 2006). Interestingly, some studies suggest that compensatory mechanisms that are believed to protect psychosis-prone individuals from developing a full-blown psychosis, may do so by limiting the upregulation of striatal dopaminergic system in response to frontal hypodopaminergia, and thus allowing for greater prefrontal activity (Krummenacher, Mohr, et al. 2010; Mohr et al. 2004; Siever & Davis 2004).

2. The role of glutamate and NMDA receptors

One of the weaknesses of the dopamine hypothesis is the fact D_2 receptor antagonists show poor efficacy when it comes to alleviating negative and cognitive symptoms (Frohlich et al. 2014). In contrast, it has been shown that modulation of the glutamate system has an effect on both cognition and positive symptoms (Corlett et al. 2011). This prompted the development of a hypothesis revolving around the glutamate system and psychosis. Glutamate binds to metabotropic receptors and three kinds of ionotropic receptors; N-methyl D-aspartate receptors (NMDA-R), kainate receptors, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA-R) (Moghaddam & Javitt 2012). The advantage of the glutamate hypothesis in schizophrenia is that it provides mechanisms explaining both negative and positive symptoms (Javitt & Zukin 1991), without actually rejecting the involvement of the dopamine system, as NMDA-R are part of brain circuits involved in dopamine release regulation (Ham et al. 2017; Javitt 2010).

The role of glutamate has mainly been studied in the context of NMDA as some studies revealed that administration of ketamine or phencyclidine (PCP) – two NMDA-R non-competitive antagonists - could induce psychosis-like symptoms in healthy individuals (Krystal et al. 1994; Tang et al. 2015). The psychomimetic properties associated with NMDA-R blockade led researchers to develop the idea that disruption of glutamate transmission via NMDA receptors might underlie some psychotic symptoms. NMDA-R are ionotropic receptor that are activated by glutamate and allow calcium influx into nervous cells. At membrane potential a magnesium ion is bound tightly to the receptor pore, preventing the entry of any further ions (Blanke et al. 2009). When presynaptic glutamate is released in the synaptic cleft, it binds to both NMDA-R and AMPA-R. Upon

glutamate binding, AMPA-R open and allow influx of sodium ions leading to a membrane depolarisation. If the concentration of released glutamate is large enough to create a substantial depolarisation of the postsynaptic membrane, then the magnesium ion blocking NMDA-R will be displaced (Cooke & Bliss 2006). Thus, when high concentrations of presynaptic glutamate are delivered on a strongly activated post-synaptic membrane, then NMDA-R open and calcium ions flow through the channel. This mechanism has been associated with the induction of long-term potentiation/depression (Frohlich et al. 2014; Blanke et al. 2009; Adams et al. 2013; Cooke & Bliss 2006). The binding site of non-competitive NMDA-R antagonists like ketamine and PCP is located deep in the receptor channel. By binding to NMDA-R, ketamine (or PCP) prevents both the entry of calcium into the cell and the binding of glutamate to the receptor (Moghaddam & Javitt 2012). It should be kept in mind that glutamate action is not limited to NMDA-R, as it also binds to kainate receptors and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA-R) (Moghaddam & Javitt 2012). The blockade of NMDA-R leads to an accumulation of glutamate in the synaptic cleft, increasing glutamate availability to other receptors (in particular AMPA-R), and thus enhancing non-NMDA glutamate transmission involved in some other pathways (Moghaddam & Javitt 2012).

In addition, NMDA-R dysfunction has also been implicated in dysregulations in gamma amino butyric acid (GABA) cortical transmission. NMDA-R are densely distributed on GABA interneurons, which have an inhibitory effect on pyramidal neurons (Steullet et al. 2016). It was reported that in the presence of ketamine (or PCP) the excitation of GABA interneurons is limited, resulting in an increased activity of pyramidal cells (Moghaddam & Javitt 2012; Adams et al. 2013). Further supporting these observations, a specific subset of GABA neurons (chandelier neurons) in the prefrontal cortex (PFC) have been described in schizophrenia, as presenting a reduced density of GABA transporters, possibly linked to the NMDA hypofunction during development (Lewis & Lieberman 2000; Ross et al. 2006; Keshavan et al. 2008; Steullet et al. 2016). NMDA-R hypofunction thus appears to disrupt the finely regulated inhibitory/excitatory cortical balance leading to an excessive excitatory activity due to a lack of inhibition (Lisman et al. 2008). It is proposed that this frontal hyperactivity adds “noise” to the system and disrupts the ability of cortical neurons to process relevant information, which could explain some of the symptoms observed in psychosis (Moghaddam & Javitt 2012).

The kynurenine acid hypothesis has been developed as a way to explain the NMDA-R hypofunction in schizophrenia. More specifically, it posits that schizophrenia is associated with elevated level of kynurenine acid, a naturally-occurring NMDA-R and α7-nicotinic receptors antagonist (Erhardt et al. 2017). Elevated concentrations of kynurenine acid would thus have direct consequences on cholinergic and glutamatergic signalling, as well as indirect effects on dopaminergic pathways (Erhardt et al. 2017), similar to the ones described above. The kynurenine pathway is induced by pro-inflammatory signals, however the origin of this dysregulation in schizophrenia still remains unclear (Erhardt et al. 2017).

2) Predictive coding and psychotic symptoms

a. Bayesian framework

When trying to understand and conceptualise how the brain processes perceptions, it is crucial to keep in mind that our perceptions and interpretation of the world are not solely based on incoming signals from the environment. Instead, and as described by the Bayesian brain hypothesis, the brain constantly tries to predict incoming inputs based on internal models, also referred to as priors (Friston 2005). This builds on Helmholtz's idea of perception as unconscious inference, which posits that the visual system incorporates implicit prior knowledge to incoming signals, in order to make sense of the ambiguous images formed on the retina (Kersten et al. 2004). Helmholtz realised that retinal images are ambiguous due to variability related to the conditions in which they are being perceived (viewpoint, lightning, etc). As a result, depending on the angle from which it is perceived, a given object can give rise to several retinal images, while different objects can produce a similar retinal image. The brain has to make educated guesses in order to try to disambiguate this noisy perception (Mamassian & Goutcher 2001; Adams et al. 2004; Mamassian & Landy 2001). Helmholtz proposed that the brain applies previously acquired knowledge to this noisy retinal image, in order to automatically and unconsciously infer the properties of the object forming the image. After a sensory signal has entered the brain, it is compared to pre-existing expectations (i.e. predictions or priors). In case of a mismatch between the incoming input and predictions, an error message is generated, representing the

difference between the two signals, and known as the *prediction error* (PE) (Rao & Ballard 1999). In order to resolve this error, the brain will search its "collection" of pre-existing priors to find which previously encountered stimulus the novel input resembles the most. As soon as a suitable match is found, the representations associated with this specific prior are applied to the new incoming information. This unconscious analogy process allows the brain to not only circumvent the initial ambiguity and thus create a stable and meaningful image of the world, but also to generate different possible predictions regarding what is most likely going to happen next, in the given situation. This influence of prior knowledge over incoming signals is considered to be part of *top-down processes*, while the incoming input is described as *bottom-up signalling* (Kersten et al. 2004; Geisler & Kersten 2002; Kihlstrom F. 1987; Bar et al. 2009; Kersten & Yuille 2003). The Bayesian probability theory describes perception as a constructive process based on internal/generative models (Friston 2005). If one applies Bayes' formula for inverse inference to the context of visual perception, one gets the probability for the object O to be present, given the retinal image (I) (posterior probability) $p(O|I) = (\frac{p(I|O)p(O)}{p(I)})$, where $p(I|O)$ is the likelihood of forming (I) given the presence of (O), and p(O) is the probability of the presence of (O). Based on this formula it then appears that the probability of the object (O) being the cause of the present perception is a trade-off between the reliability/precision of the sensory evidence and the prior probability p(O) (Kersten et al. 2004). Thus, the more ambiguous the image features are, the more biased is the perception towards prior knowledge, and conversely, the more precise the sensory input is, the weaker is the influence of priors (Kersten & Yuille 2003; Adams et al. 2013) (Figure 3). Some perceptions rely largely on priors, for example seeing a human silhouette in the dusk. However, others are rather sensory input driven. This is the case when existing priors are either unreliable, or no longer suitable in a specific context and need to be updated (Friston 2005). The idea that Bayesian processing provides solutions that are optimal in a given situation also implies a notion of dynamic processes, allowing a representation to be modified in case of changes in the environment. Similarly, priors are not static representations. Instead, they result from constant bidirectional interactions with incoming sensory input. Previous work has reported that priors that are often referred to as being strong, such as the assumption that light comes from above, can easily be overridden by incoming input (e.g. incongruent haptic or visual signals) contradicting the idea that light may originate from above, when those are more likely to be true in a given situation (Adams

et al. 2004; Morgenstern et al. 2011). This highlights the dynamic and adaptive nature of priors.

Similar to the idea proposed by Helmholtz, the Bayesian brain hypothesis describes the brain as an inference machine that combines prior knowledge with incoming information, in order to optimise probabilistic representations of causes underlying perceived items. In this framework, information processing is conceptualised as a hierarchical or an aggregational pyramidal structure. The base involves processing of simple sensory input in primary sensory cortex, moving towards networks associated with information processing of increasing levels of complexity/abstraction, in areas increasingly distant from sensory input (Taylor et al. 2015; Friston 2010; Friston 2005; Mumford 1992). Generative models of the world are created via PE and interactions between the different hierarchical levels. The underlying concept is that each hierarchical level interacts with the levels below and above it. When an incoming sensory input does not match the pre-existing expectations, a PE is

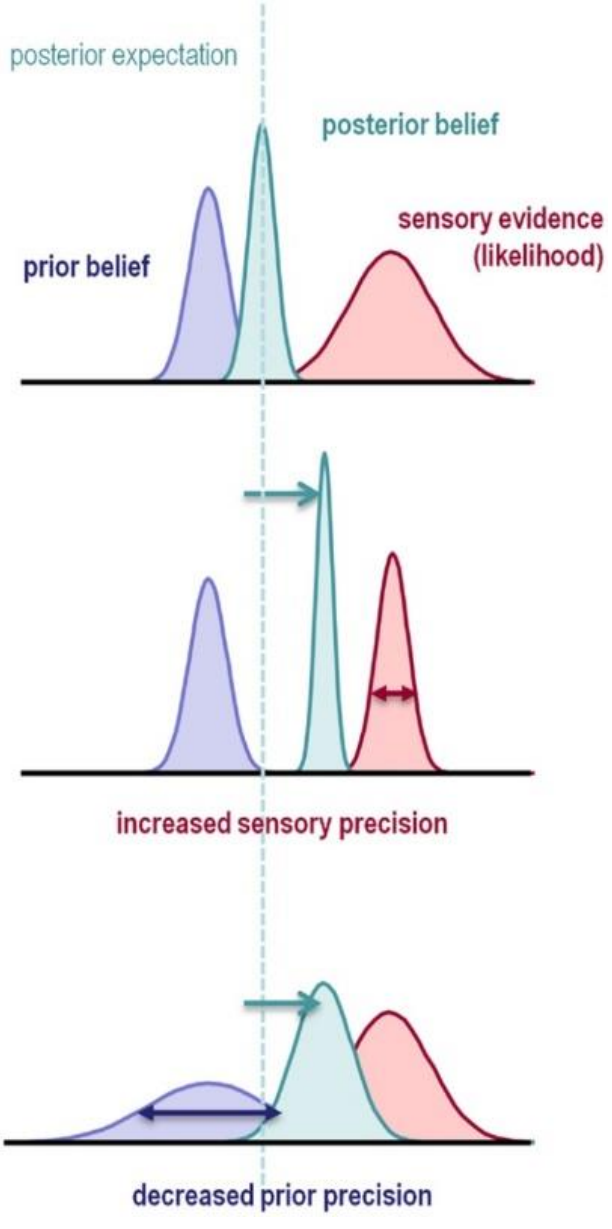

Figure 3. Schema of the influence of signal precision on generation of posterior belief. Gaussian probability distributions representing prior beliefs, posterior beliefs, and sensory evidence as functions of some hidden (unknown) parameter. The width of the distributions symbolises their dispersion or variance and is the inverse of the associated precision. The dotted line represents the posterior expectation. The posterior belief is biased toward the prior belief or the sensory evidence, in proportion to their relative precision. As shown here, if the prior belief has a larger precision than the sensory evidence, the resulting posterior belief tends to be closer to the prior expectation (top panel). Conversely, the posterior belief will be biased towards sensory evidence if the precision of sensory evidence increases (or fails to be attenuated) (middle panel), or the precision of the prior belief decreases (bottom panel). Reprinted from Adams, Stephan, Brown, Frith and Friston Copyright©2013, with permission from Frontier Psychiatry

generated at the entry level (Friston 2005; Rao & Ballard 1999). The brain first tries to resolve it at that level, using feedback from the immediate higher level (top-down influence of priors). If this attempt fails, the residual PE is transmitted, in a bottom-up fashion, to the next higher level where a more complex prior is used to try to reduce the PE signal. This process continues until the PE is successfully minimised (Rao & Ballard 1999). This implies that a given level can be both a source of bottom-up signalling (sending PE to the next higher level) and a source of top-down signalling (sending feedback/priors to the level below) (Sterzer et al. 2016). For simplification purposes, in terms of processing complexity low-level hierarchies usually refer to primary sensory cortices; i.e. the initial entry level of sensory information. The higher up in the network the signal is moving forward along this hierarchy, the more complex and integrated is the processing systems.

An example of how the Bayesian brain hypothesis may be applied to the experience of reality is the experience of the self (Seth 2013; Apps & Tsakiris 2014). *Self-recognition* relies on the ability to experience a border between the self and the external world. The conscious experience of one's own body in relation to the external world is thought to depend on two main, closely intertwined, cognitive components: the sense of body-ownership (the feeling of inhabiting/experiencing one's own body) and the sense of agency (the subjective awareness that one is initiating, executing, and controlling one's own volitional actions in the world) (Tsakiris et al. 2007; Jeannerod 2003). Both are considered automatic, non-conceptual signals, relying on an interplay between bottom-up sensory input and top-down low-level bodily representations (Klaver & Dijkerman 2016; Tsakiris 2016). Unexpected stimuli may bear threats to the organism's integrity. Therefore, from an evolutionary/survival point of view, experiences that can be predicted are less relevant than surprising events (Blakemore et al. 1998). Put simply, since the brain's processing resources are limited, unpredictable stimuli should be prioritised over predictable signals in order to have an efficient processing system. Thus, being able to differentiate self-generated, and therefore predictable, from externally generated elements is crucial.

The idea that the brain uses motor predictions in information processing started in the 1950s with the work on the visual system by Sperry (Sperry 1950), and Von Holst and Mittelstaedt (von Holst & Mittelstaedt 1950; Holst & Mittelstaedt 1971). Those studies

suggested that the brain can correct for the movement of the eyes when experiencing visual input by using predictions - leading to a stable visual experience of the external world. More recently, it has been suggested that the brain uses predictions to attenuate the sensory experience based on sensory input that is internally produced when moving (Pynn & DeSouza 2013; Niziolek et al. 2013; Feinberg 1978; Blakemore, Wolpert, et al. 2000; Shergill 2003). Thereby, self-produced touch can be differentiated from externally induced sensory input – a phenomenon that explains why it is hard to tickle oneself (Blakemore, Wolpert, et al. 2000). In more detail, the hypothesis suggests that when the brain decides to execute a movement, it sends a motor command to the motor system and an sensory prediction of the action to sensory cortex (Ford & Mathalon 2005). The motor command sent to the motor system leads to the movement execution, while the signal sent to the corresponding sensory cortices (the so-called efference copy or corollary discharge) allows the brain to predict the sensory consequences of upcoming movements and thus to alter its response to the associated feedback (Figure 4). The processing of predicted incoming signals is attenuated, allowing the brain to use more resources to surprising events. Due to the importance of motor predictions in these mechanisms, a functional low-level prediction system is key in the experience of self-recognition. It should be noted that in addition to the predicted sensory consequences of a movement, the movement initiation also generates an intention component, which is crucial in the emergence of a sense of agency.

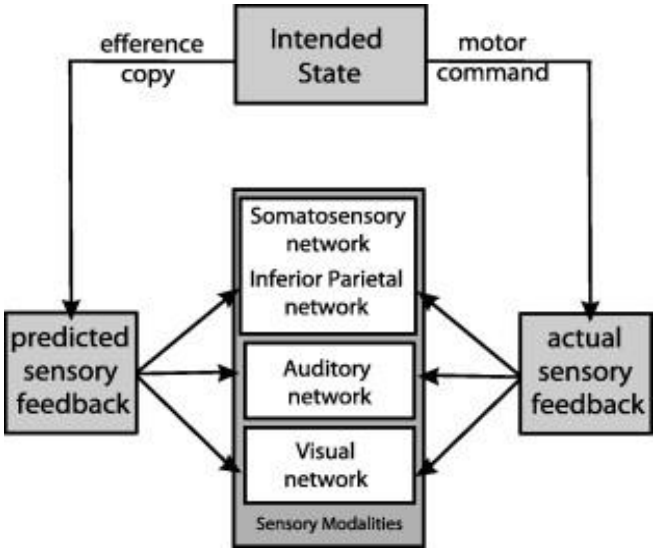

Figure 4. Mechanisms involved in motor execution. Reprinted from *The function of efference copy signals: Implications for symptoms of schizophrenia,* Pynn L & DeSouza, J, 124-133, Copyright©2003, with permission from Elsevier

Similarly to the sense of agency, *body ownership* (the feeling that one's body belongs to oneself - e.g. "this is my hand" - and the sense that other objects/bodies do not) require a functional prediction system as it relies on internal body representations (body map) that act as low-level top-down modulators (Tsakiris 2016; Klaver & Dijkerman 2016).

b. Psychosis and the prediction system

As mentioned earlier, schizophrenia is a severe clinical condition that presents a wide range of symptoms, out of which psychotic symptoms are most characteristic. Although the mechanisms underlying delusions and hallucinations are still unclear, a growing body of evidence points towards impairments in brain systems dealing with perceptions and expectations. More specifically, it seems that a change in the top-down/bottom-up balance of information processing is at the core of psychotic symptoms (Adams et al. 2013; Fletcher & Frith 2009; Corlett et al. 2009). While low-level predictions have been described as noisy and unstable, leading to an increased influence of bottom-up signals, higher-level predictions appear overly stable and inflexible, resulting in an abnormally strong influence of beliefs over perceptions.

1. Imprecise low-level prior beliefs and aberrant salience

1.1 External input

There is a growing body of evidence in schizophrenia research linking impairments in low-level prediction system to dysregulation of the dopamine system and its role in salience attribution (Kapur 2003; Howes & Kapur 2009; Winton-Brown et al. 2014). Studies using amphetamine challenge - a procedure that results in a dopamine transmission (Calipari & Ferris 2013; Fleckenstein et al. 2007) - revealed schizophrenia patients, and to a lesser extent schizotypal individuals (Abi-Dargham et al. 2004; Woodward et al. 2011), were characterised by an abnormally elevated dopamine transmission (Breier et al. 1997; Laruelle et al. 1996). In line with the idea of an excessive dopamine signalling in schizophrenia, several studies then proposed that instead of being stimulus-driven, dopamine transmission is erratically triggered in psychotic patients (Van Der Gaag 2006; Kapur 2003; Howes & Kapur 2009; Roiser et al. 2009). It was proposed that context-irrelevant stimuli that should be ignored are wrongly assigned salience (referred to as *aberrant salience* or *hypersalience* in case of excessive salience attribution) (Kapur 2003; Winton-Brown et al. 2014). Signals that should have been disregarded early on, reach the prefrontal cortex, leading to conscious processing of the information, making it appear as an important event (Braver et al. 1999). In phenomenological terms, this phenomenon is referred to as *hyper-reflexivity*

(Sass & Parnas 2003; Sass et al. 2013; Pérez-Álvarez et al. 2016), "a type of intensified self-consciousness, in which aspects of oneself that are normally or functionally unnoticed, pre-reflective, tacit or implicit, are objectivised and experienced as objects of consciousness"(Pérez-Álvarez et al. 2016).

In Bayesian terms, this translates into having elements of background noise acquire aberrantly high precision (Adams et al. 2013; Sterzer et al. 2016; Kapur 2003). For instance, patients might report paying more attention to things they used to ignore; "My senses were sharpened. I became fascinated by the little insignificant things around me" (Bowers & Freedman 1966). "My senses seemed alive, colours were very bright, they hit me harder. Things appeared clear-cut, I noticed things I had never noticed before" (Bowers 1968). Such a chaotic and random salience attribution also renders learning difficult, as those aberrant sensory signals keep overriding each other (Adams et al. 2013), and get incorporated in newly updated cognitive models of the world. If this repeats frequently, those internal models get modified continuously, eventually preventing patients from building reliable and stable sets of cognitive representations of the world (Fletcher & Frith 2009), at least in lower hierarchical levels. The oddball paradigm is a good example of this phenomenon. In this paradigm, subjects are presented with a sequence of frequent distracting, identical stimuli interspersed with rare (different) target stimuli. A change in brain activity referred to as mismatch negativity (MMN - usually measured in the form of brain event-related potentials - ERP) is elicited by any discriminable change when the target stimuli are compared with the repeated stimuli (Winkler et al. 1996). This change in activity is assumed to represent transient memory traces (Ritter et al. 1995) that supposedly reside in lower hierarchal levels. An appropriate transient memory trace allows to predict the occurrence of the frequent stimuli and to decrease the salience of these stimuli in a top-down regulatory fashion (by analogy with the efference copy system). Previous studies have reported a significantly decreased ERP change in schizophrenia (Javitt et al. 1998; Javitt et al. 1993), suggesting impairment in the formation of those short-term memory traces. Schizophrenia patients' failure to build reliable memory trace prevents them from accurately differentiating repeated stimuli from deviant ones, hence the observed decreased MMN. Put differently; patients experience both deviant and recurring stimuli as novel and unpredicted. In addition, the memory trace may be associated to expectations or priors in lower hierarchical levels. Interestingly, such impairments are

also reported in prodromal and at-risk individuals (Brockhaus-Dumke et al. 2005; Atkinson et al. 2012), as well as patients' first-degree relatives (Jessen et al. 2001). Also, recent studies have suggested that MMN could be used in order to predict who will develop a clinical psychotic syndrome in at-risk populations (Näätänen et al. 2016).

A failure in constructing low-level priors in a bottom-up fashion is also apparent in sensory and sensorimotor processes in schizophrenia. Based on the same concept of brain habituation to repeated stimuli in order to optimise the brain processing capacity, it has been shown that the presentation of a first, weak stimulus (prepulse) attenuates the response to a second, stronger stimulus (pulse), provided the time interval between the two is between 30 and 500 milliseconds (Braff et al. 1992; Swerdlow et al. 2006; Javitt & Freedman 2015). This reduced response, also referred to as sensory/sensorimotor gating, can be quantified in two ways. First, this can be achieved by measuring the acoustic startle reflex (i.e. blinking) using electromyography (Braff et al. 1992). The reduced startle response to the second stimulus, when preceded by a weaker prepulse is referred to as prepulse inhibition (PPIn) (Braff et al. 1992; Swerdlow et al. 2006; Javitt & Freedman 2015). Deficits in PPIn have been repeatedly reported in schizophrenia patients and represent one of the most consistent behavioural markers of the disorder (Swerdlow et al. 2006; Javitt & Freedman 2015; Braff et al. 1992). Another approach is based on auditory evoked potentials. The first largest response to an auditory stimulus is a positive wave appearing 50 milliseconds after the stimulus onset and is called the P50 potential (Siegel et al. 1984; Javitt & Freedman 2015). In healthy participants, due to the habituation phenomenon the P50 response to the second stimulus (pulse) is smaller than P50 response to the first signal (Siegel et al. 1984). Deficits in P50 attenuation have also been observed in schizophrenia (Siegel et al. 1984; Javitt & Freedman 2015). Interestingly, similar deficits in both PPIn and P50 attenuation have been reported in people with schizotypal personality and schizophrenia patients' relatives (Giakoumaki 2012; Clementz et al. 1998; Javitt & Freedman 2015; Siegel et al. 1984), suggesting these impairments are part of a trait and not state-dependent. The deficits in MMN, PPIn and P50 brings support to the idea psychosis and psychosis-proneness are associated with deficits in the bottom-up generation of low-level priors.

Aversive conditioning (Balog et al. 2013; Holt et al. 2009; Jensen et al. 2008; Romaniuk

et al. 2010; Holt et al. 2012), reward learning (Murray et al. 2008; Roiser et al. 2009; Schlagenhauf et al. 2014) and associative learning (Corlett & Fletcher 2012; Corlett et al. 2007) represent more complex forms of learning relying on bottom-up sensory processes, which have also been reported as abnormal and weakened in schizophrenia. It is argued that such learning deficits are also related to failure to form reliable low-level priors based on incoming sensory signals (Hofer et al. 2001).

This deficit in generating reliable priors also implies that in certain situations schizophrenia patients and psychosis-prone individuals tend to experience the world in a more accurate way as their perceptions are less constrained by priors. A study investigating perceptual biases in paranormal believers (that can be compared to delusion-prone individuals) versus sceptics found that in a situation of high perceptual ambiguity and in presence of two equally probable high-level priors (thus comparable to a context with no reliable high-level priors), sceptics were more biased towards one of the two priors while paranormal believers remained at chance level (Van Elk 2015). This is in line with the observation that, when facing perceptual ambiguity in the absence of reliable pre-existing priors to bias their perceptions, delusion-prone individuals rely more extensively on incoming signals. This can also be put in parallel to the hollow-mask illusion, an illusion building on the use of prior perceptual knowledge regarding three-dimensional shape of faces, as well as general rules of perception, such as Gestalt laws of organisation and perspective (Dima et al. 2009). In this illusion, the convex and concave (hollow) sides of a rotating mask are shown alternatively. However, the bias of seeing faces as convex is so strong it actually overwrites contradicting sensory evidence signalling that the mask is hollow, and people experience the hollow side as convex (R L Gregory 1997; Richard L. Gregory 1997). Interestingly, patients with schizophrenia tend to be more accurate than controls, by perceiving more frequently the hollow side as concave, suggesting a larger influence of bottom-up input and greater difficulties in using top-down signals (knowledge about face perception) in schizophrenia patients (Keane et al. 2016; Dima et al. 2009).

1.2 Internal input

Importantly, the consequences of impaired low-level priors are not limited to external input; they also apply to internally generated signals. In line with this idea,

dysfunctional low-level predictive processes have been proposed as underlying hallucinations and self-recognition deficits observed in psychotic patients (Fletcher & Frith 2009; Notredame et al. 2014; Horga et al. 2014). As mentioned previously, self-recognition relies on the ability to experience a border between the self and the external world, or put in predictive coding terms; between "the expected" self-generated input (associated with intentions and efference copy) and "the unexpected" externally generated input. It has been shown that psychosis patients experiencing auditory hallucinations and passivity cannot cancel self-induced sensory experience such as tickling (Blakemore, Smith, et al. 2000) as observed in healthy subjects (Blakemore et al. 1998). Moreover, failure to attenuate sensory consequences of self-generated actions in schizophrenia was elegantly shown by Shergill and colleagues, in a study using the force-matching task in schizophrenia patients (Shergill et al. 2005). The force-matching task was previously developed by the same group to show that the sensory perception is attenuated during self-generated actions (Shergill 2003). One particularity of this paradigm is that, a fully functional prediction system actually may hinder accurate performance. In this task, a mechanical force is applied to the finger of a participant, who is then asked to reproduce the same force intensity by applying it on her/his finger either by doing it directly with her/his other hand, or by using a joystick (Figure 5). Shergill et *al* reported that while control participants were accurate in reproducing the force when using the joystick, they underestimated the force they applied when using their index finger, leading them to apply a greater force than the actual one, in line with the sensory attenuation associated with self-generated actions described above. Apart from replicating the results from the initial experiment (Shergill 2003) they observed that although both groups were performing equally well in the "joystick condition", schizophrenia patients were much more accurate than controls when using their own finger to reproduce the force. This increased accuracy in force matching reflects a decreased sensory attenuation in schizophrenia patients, related to dysfunctional sensory (low-level) predictive processes. These results were replicated a couple of years later in a delusion-prone population (Teufel et al. 2010), confirming the association between impairments in low-level prediction systems and the psychosis spectrum.

Impaired self-recognition is one of the consequences of faulty low-level predictive processes we decided to investigate in our research work. From a behavioural or

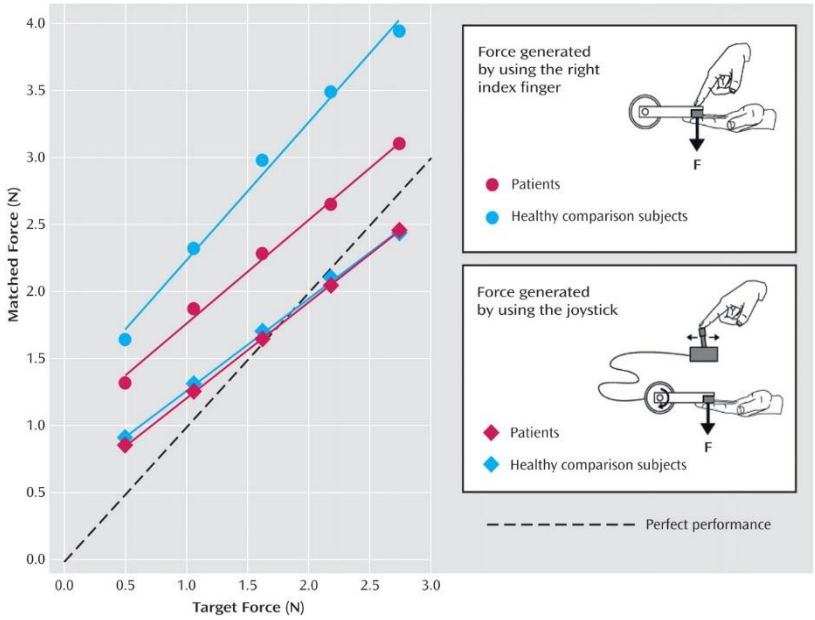

Figure 5. Matching Force Generated by 19 Patients With Schizophrenia and 19 Healthy Volunteers Using the Right Index Finger or Joystick as a Function of the Externally Generated Target Force[a]

[a]Dotted line represents perfect performance. On each trial the torque motor generated a force between 0.5 and 2.75 Newtons on the left index finger for 3 seconds (80 trials in a pseudo-randomized order). Subjects were then required to reproduce the force either by pushing with their right index finger or by using a joystick that controlled the torque motor. Each subject participated in both conditions in a counterbalanced order. The applied forces were measured by using a force transducer mounted in the lever of the torque motor. *From Sukhwinder et al, 2005. Reprinted with permission from The American Journal of Psychiatry, Copyright©2005. American Psychiatric Association. All Rights Reserved.*

clinical perspective, such perturbations in the low-level systems (in that case, the efference copy system and internal body maps) result in impairments in the experience of body awareness, which manifest as more malleable body representations, blurrier experience of body borders, or aberrant feeling of agency. Schizophrenia patients describe such experiences in various terms, as reported in phenomenological studies. For instance, a patient declared she felt as if she "walked stiffly and did not know how to hold [her] hands"(Ferri et al. 2012), while another expressed his current feeling as: "I am no longer myself […] I feel strange, I am no longer in my body, it is someone else; I sense my body but it is far away, some other place. Here are my legs, my hands, I can also feel my head, but cannot find it again. I hear my voice when I speak, but the voice seems to originate from some other place. […] Am I here or there? Am I here or behind?" (Parnas & Handest 2003). Such disturbed bodily experiences could be reproduced in experimental settings using paradigms building on bodily perceptions. The most commonly used one is the Rubber Hand Illusion (RHI). In this paradigm, a participant is tricked to feel ownership over a rubber model hand, by placing the fake hand in front of a participant whilst her/his own hand is hidden from view. Using two small brushes, the experimenter strokes both hands simultaneously. This elicits a feeling of ownership over the fake hand and a shift toward

the rubber hand in the perception of the participant's hand location (Botvinick & Cohen 1998). While such bodily illusions are reported in healthy individuals (Botvinick & Cohen 1998), they are reported as stronger in both schizophrenia patients (Thakkar et al. 2011; Klaver & Dijkerman 2016; Peled et al. 2003) and psychosis-prone individuals (Germine et al. 2013; Louzolo et al. 2015).

Other positive symptoms are also thought to relate to impairments involved in self-recognition processes. Delusions of control, the feeling that one's own movements are being controlled by an external force (Frith et al. 2000), are viewed as stemming from a deficit in the integration of the predicted sensory consequences of an action (Frith et al. 2000). If this part of the motor action process was lost, a self-generated movement would feel alien, and externally-generated. Individuals experiencing those phenomena may then try to explain them by assuming other people or external forces are controlling them (Frith et al. 2000). Auditory verbal hallucinations (AVH), the experience of hearing speech in the absence of any external stimulation (Jones & Fernyhough 2007), and delusion of thought insertion (a particularly striking form of self-disturbance, frequently reported in schizophrenia) (Sterzer et al. 2016) are also viewed as a failure in self-monitoring of inner speech (Vercammen et al. 2010; Waters et al. 2012; Gould 1949; Bick & Kinsbourne 1987; Horga et al. 2014; Jardri et al. 2016; Allen et al. 2007; McGuire et al. 1995). A mechanism similar to the one described in delusion of control is thought to underlie these phenomena, but instead of a failure to predict sensory consequences of a motor action, the deficit relates to inner speech and though processes (Jones & Fernyhough 2007; Sterzer et al. 2016). These studies stress the importance of understanding the mechanisms that lead to a dysfunctional efference copy system.

2. Inflexible high-level prior beliefs

As mentioned previously, delusions are inflexible erroneous idiosyncratic beliefs (high-level priors) (Fletcher & Frith 2009; Coltheart et al. 2011; Eisenacher & Zink 2016; Woodward et al. 2008). This suggests that, in terms of predictive coding, psychosis is associated with high precision high-level priors. This high precision renders the priors difficult to change and may lead to a larger top-down influence of these beliefs on perceptions (Adams et al. 2013). The inflexible nature of delusions has been

reproduced experimentally by studies investigating schizophrenia patients' ability to assess the likelihood of statements or short scenarios with increasing degrees of implausibility, and to update their judgements accordingly. This body of research revealed schizophrenia patients' tendency to stick longer to initial beliefs, even in the face of contradicting evidence; the so-called *bias against disconfirmatory evidence* (BADE – i.e. the tendency to disregard evidence that goes against the current assumption) (Woodward et al. 2008; Moritz & Woodward 2006; Veckenstedt et al. 2011; Woodward et al. 2006; McLean et al. 2016). This bias was also observed in non-clinical delusion-prone populations (Buchy et al. 2007; Woodward et al. 2007; Orenes et al. 2012). Recent studies have complemented these observations by showing that psychosis-related states were associated with an increased effect of high-level priors on perceptions (Schmack et al. 2013; Teufel et al. 2015). More specifically, in comparison with control individuals, it has been suggested that when schizophrenia patients (Teufel et al. 2015) and delusion-prone individuals (Schmack et al. 2013; Teufel et al. 2015) are confronted to ambiguous perceptual stimuli, their perceptions are strongly biased towards beliefs they have acquired beforehand from specific visual or verbal instructions.

It might seem paradoxical that both an unstable (imprecise) prediction system and an overly stable (precise) prediction system may coexist in the same individuals. A common tentative explanation is to view them as causally related; one triggering the other (Kapur 2003; Corlett et al. 2010). As mentioned above, psychosis patients appear to have a noisy low-level system, preventing them from building reliable priors. The constant change in those predictions, the repeated appearance of background noise elements into conscious processing and the associated disturbances in self-recognition, all lead to an unsettling experience for the individual, rendering the world very unpredictable (Kapur 2003; Adams et al. 2013). Delusions may be conceptualised as a cognitive effort by patients to make sense out of those strange experiences and create a somewhat coherent model of the world (both external and internal) in order to reduce cognitive dissonance (Kapur 2003; Corlett et al. 2010). Corlett and colleagues furthered Kapur's idea of delusions as a top-down cognitive explanation used to make sense of aberrant salience (Kapur 2003), by suggesting delusions correspond to false inferences about the world, stemming from a failure in encoding uncertainty about sensory information (Corlett et al. 2010). While both Kapur and Corlett *et al* present delusions

as a secondary effect of aberrant salience (Kapur 2003; Corlett et al. 2010), we are slightly challenging this view in the present thesis (***Study IV***), by suggesting that delusions are not simply a passive adaptive consequence of a deficient low-level prediction system (Kapur 2003), but also represent a proactive strategy to over-integrate explicit information at a high-level, and use it to interpret a noisy environment. However, the exact mechanisms underlying belief inflexibility observed in psychosis-related states still remain unclear.

II – Aim and hypotheses

a. Study I

Building on the well-documented self-awareness disturbances in psychosis-related states, ***Study I*** aimed to test to what extent delusion-proneness was associated with impairment in terms of self-recognition (both body ownership and agency) and to investigate whether these impairments were related to the hypersalience hypothesis and/or an impaired low-level prediction system.

We used the active Rubber Hand Illusion (RHI) paradigm (Kalckert & Ehrsson 2012) as it relies on perceptual and cognitive mechanisms related to bodily-awareness, thus making it an ecologically relevant paradigm in the context of self-awareness disturbances. While impairments in some processes related to self-recognition (i.e. efference copy) had been previously reported in delusion-prone individuals (Teufel et al. 2010), the relation between these disrupted processes and sense of agency/ownership had not been investigated in psychosis-proneness.

Previous studies using an active condition in the RHI paradigm reported a strong increase in the experience of agency in the active condition compared to the passive one (Kalckert & Ehrsson 2012; Dummer et al. 2009). The difference between passive and active conditions lies in the fact the latter is the only condition involving motor predictions (intentional signals and efference copy). We argue that motor predictions are thought to pertain to the lower end of the processing hierarchy. If delusion-prone individuals are indeed characterised by a faulty low-level prediction system, their experience of the active and the passive conditions (in terms of sense of ownership and agency) should not differ much. We thus hypothesised that delusion-proneness would be associated with a smaller increase in agency for active versus passive movements. We also expected a similar, though more limited, effect in terms of ownership.

b. Study II

Overlaps between psychosis and ADHD/ASD tendencies have been reported previously (Pallanti & Salerno 2015; Dalsgaard et al. 2014; Stahlberg et al. 2004; Cederlöf et al.

2016; Chisholm et al. 2015; de Lacy & King 2013; Stone & Iguchi 2011; Sullivan et al. 2012). This can have important implications when studying psychosis-proneness, because some results observed in delusion-prone individuals might actually be associated with ADHD or ASD tendencies rather than psychosis-related mechanisms. It is thus crucial to take those traits into account when studying delusion-proneness, specifically.

Study II used a large healthy male population (n=925) to explore the relation between delusion-proneness, ADHD- and ASD-traits. We first investigated the extent to which ADHD and ASD traits correlated with delusion-proneness in a healthy male population. In a second step, we aimed to identify which prototypical dimensions in the ADHD and ASD traits were related to delusion-proneness. We hypothesised that delusion-proneness scores would correlate positively with ASRS and AQ scores, and that these relations would remain when limiting the analyses to prototypical items.

c. Study III

Study III builds on the similarities between delusion-like behaviours and the phenomenon of confabulation observed in schizophrenia (Fotopoulou et al. 2007). Here, we aimed to study whether delusion-prone individuals showed an increased tendency to accept false feedback - a behaviour that has been shown to be linked to confabulation - when facing perceptual ambiguity.

Unlike confabulations in memory-related disorders like Alzheimer or Korsakoff syndrome, that correspond to an attempt from the brain to fill in blanks and make sense of scattered memories (Talland 1961), confabulations associated with psychosis are considered to be related to formal thought disorder. These confabulations rather originate from a reconstruction/reorganisation of thoughts. Earlier work showed that, such confabulations include some elements that were present in the original story that was provided to the patients (Shakeel & Docherty 2015; Nathaniel-James & Frith 1996). As mentioned previously delusions are unshakable and erroneous idiosyncratic beliefs usually used to explain away some strange experiences (Kapur 2003). Despite their unsubstantiated nature and content bizarreness, delusional beliefs do incorporate some elements that are present in patients' life or society, or that patients got to know

or read about. Delusions and psychosis-related confabulations thus seem to share some similarities (Shakeel & Docherty 2015). They both involve the production of unfounded claims, devoid of the intent to deceive others. In addition these claims are inadequately evaluated, leading to a failure to reject them even in face of contradictory evidence (Turner & Coltheart 2010). Instead, they are actually associated with the production of secondary supporting claims (Turner & Coltheart 2010).

In order to study whether delusion-prone individuals displayed an increased tendency to accept false feedback (also referred to as *liberal acceptance bias*) (Moritz & Woodward 2004; McLean et al. 2016; Moritz et al. 2009), we used a modified version of the choice blindness(Johansson et al. 2005), a paradigm that challenges the reliability of low/intermediate-level priors and leads to the induction of confabulation. Choice blindness has been shown to be closely related to confabulations (Johansson et al., 2005) and therefore served as a proxy for confabulations.

d. Study IV

As discussed previously, a paradox in psychosis research lies in the fact patients with psychosis seem to have both imprecise low-level priors and overly precise high -level priors. The different levels of the processing hierarchy interact closely, so in order to try to get a better understanding of the low- versus high-level paradox, it is preferable to study both ends of the hierarchy together, rather than in isolation. This was the specific aim in ***Study IV***. As opposed to ***Study I*** and ***Study III*** that initially focused on the lower end of the processing hierarchy, ***Study IV*** allowed us to tap separately on both low- and high-levels, in the context of complex cognitive processing (i.e. social judgement related to fear learning). To our knowledge, this was the first time such a paradigm was used with a delusion-prone population.

Using a combination of classical fear conditioning (bottom-up low-level processes) and instructed fear learning (top-down high-level beliefs) (Olsson & Phelps 2004; Olsson & Phelps 2007), we first aimed to show a double dissociation in delusion-prone participants. Namely, we hypothesised that delusion-prone individuals would be impaired in the condition relying on low-level priors (i.e. classical fear conditioning – non-instructed conditioning), while they would show a larger influence of high-level

priors (i.e. instructed conditioning) than controls. In terms of behaviour this would translate into delusion-prone individuals showing reduced evaluative conditioning and autonomic responses to non-instructed conditioned stimuli (classical fear conditioning), as shown in previous studies on psychosis-related states (Balog et al. 2013; Holt et al. 2012; Holt et al. 2009; Jensen et al. 2008; Romaniuk et al. 2010), while a normal conditioned response pattern would be restored, or even more strongly expressed, when verbal instructions regarding the conditioned stimuli would be provided prior to the conditioning phase.

Since we were also interested in the mechanisms underlying the influence of high-level beliefs on lower-level processes related to fear learning (Olsson & Phelps 2004; Olsson & Phelps 2007), we used functional magnetic resonance imaging (fMRI) in order to investigate whether differences were also observed in terms of brain activity in regions related to high-level expectations. We expected the prefrontal cortex, and more specifically the lateral orbito-frontal cortex (lOfc), to be involved, as these regions have been reported in cognitive reappraisal (Wager et al. 2008) as well as expectation-related processes, like placebo effect (Petrovic et al. 2010; Petrovic et al. 2002; Petrovic et al. 2005). Building on Schmack's study on the influence of high-level expectations on sensory processing, where an association between sensory processing and lOfc was reported in delusion-prone individuals (Schmack et al. 2013), we hypothesised group differences in terms of activity in this region (lOfc), and in terms of interaction between lOfc and the main areas involved in fear and pain processing.

III - Methods

a. Questionnaires

1. Peters' Delusion Inventory

As discussed previously, in order to try to have a better and more thorough understanding of the mechanisms underlying psychosis it is important not to limit research to clinical populations but to also investigate populations that are at-risk or prone to psychosis. Therefore, we adopted this approach in the present work. In order to identify individuals showing delusion-proneness, we used Peters' Delusion Inventory (PDI) (Peters et al. 2004). PDI is a questionnaire designed to assess delusional ideation in the normal population (Peters, Joseph, et al. 1999). In its original form, the questionnaire contained 40 items. A shorter version containing 21 items of the original questionnaire was later developed (Peters et al. 2004). This is the version we used in our studies. Items are in the form of questions investigating the presence of different psychosis-related experiences (e.g. paranoia, paranormal belief, thought disturbances, and so forth - see appendix). In addition to evaluating delusional ideation, the questionnaire also takes into account the level of conviction, preoccupation, and distress associated with the belief. These dimensions respectively turn into conviction, preoccupation and distress scores. For each endorsed item, people have to rate on a 5-point Likert-scale (1 to 5) how convinced, preoccupied and distressed they are by the given experience. These sub-scores are interesting as they give a more detailed picture of the delusion-proneness of an individual. We argue that the distress dimension is particularly interesting as it has been reported main factor differentiating clinical population from at-risk populations (Peters, Day, et al. 1999; Lim et al. 2011).

In ***Study I***, a dimensional approach to delusion-proneness was implemented, as we were interested in studying delusion-proneness as a whole. Therefore, the participants were not pooled into groups. The main analyses consisted of correlations between ownership/agency ratings and PDI Yes/No scores. Similarly, in ***Study II*** we used this dimensional approach, as we were interested in relations between delusion-proneness and ADHD/ASD traits.

In ***Study III*** and ***Study IV*** on the other hand, we included two groups, i.e. a control group

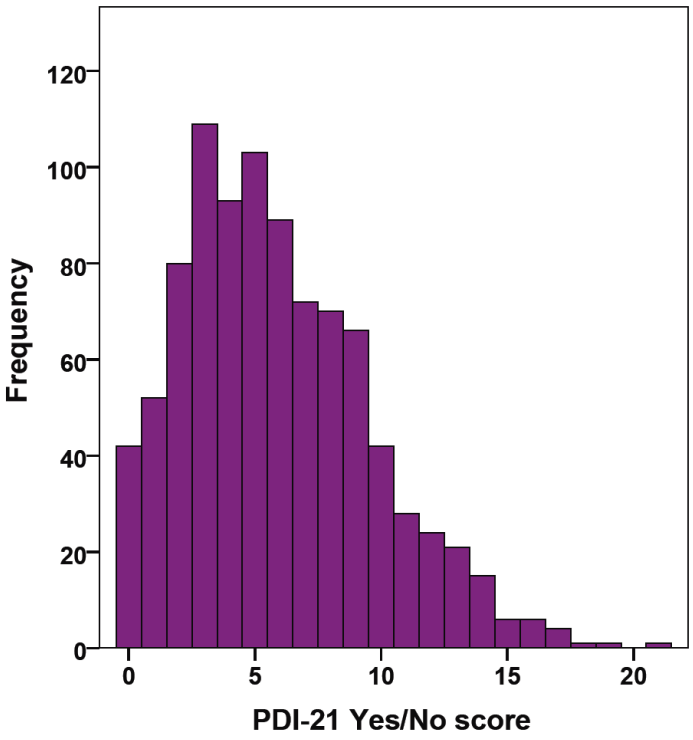

Figure 6. Distribution of PDI Yes/No scores in our sample of 925 healthy male participants. Participants were recruited via social media and filled in the questionnaire online – ***Study II and IV***

and a delusion-prone group, in the analyses in order to ensure to include highly delusion-prone individuals (in Study III we started with a dimensional approach but changed it to a group approach given the limited number of delusion-prone subjects in the sample). Participants were selected based on their Yes/No score. Due to the skewed distribution of PDI, we needed to screen a large number of individuals in order to find enough people with a PDI-score above 10 for ***Study III***. In total we gathered data on 925 male healthy participants aged 18 to 35 (mean=24.98 years, SD=0.161). The distribution of the Yes/No score (Figure 6) was quite similar to the one reported in Peters' original study on the 21-item version of the questionnaire (Peters et al. 2004). In ***Study II*** we used the data we gathered on these 925 participants, in order to study the relation between delusion-proneness and ADHD-/ASD-traits.

2. Adult ADHD Self-Report Scale

In order to estimate ADHD tendencies we used the Adult ADHD Self-Report Scale (ASRS), a self-report screening scale developed by the World Health Organization, in order to measure ADHD tendencies and to be used as a part of a clinical ADHD-assessments in adult individuals (Kessler et al. 2005). The questionnaire contains 18 questions. Using a 5-point Likert scale, participants have to report how frequently a particular symptom of ADHD has occurred to them over the past 6 months. The responses range from never (0), rarely (1), sometimes (2), often (3), to very often (4), to a total score range from 0 to 72. The questionnaire can be divided into two parts

(part A/part B) out of which part A is used as a screening tool. In the present study, we used the full questionnaire (18 questions) and we ran our analyses on the summed frequency scores (referred to as the total ASRS score). We used the screening part (part A) in a sub-analysis, in order to exclude individuals that possibly show relevant symptoms.

3. Autism Quotient

Autism spectrum disorder (ASD) tendencies were estimated with the Autism Quotient (AQ); a self-administered questionnaire developed in order to assess the degree to which an adult individual is displaying autistic traits (Baron-Cohen et al. 2001). The 50 items of the questionnaire can be grouped into five subscales (10 questions each) that target social skills, attention switching, attention to detail, communication and imagination, and for a maximum score of 50 points. The higher the score, the stronger autistic-like behaviour tendencies. A score of 32 is considered as a cut-off distinguishing individuals with a clinically significant levels of autistic traits (Baron-Cohen et al. 2001).

4. Factor analysis on self-report questionnaires

In order to identify which dimensions of ADHD and ASD traits were correlating most strongly with delusion-proneness we conducted a factor analysis (exploratory structural equation modelling (Marsh et al. 2014)) on all the items of the three questionnaires put together. This method consists in applying an exploratory search for a restricted number of factors and then testing the fit of the model with a confirmatory approach. We started the analysis with a 3-factor model and ran it until an acceptable model fit was reached (RMSEA under 0.06 and a CFI over 0.95 (Brown 2015)). We then studied correlations between all the factors of the best fitting model.

b. Active Rubber Hand Illusion

The active RHI is a modified version of the classical RHI (Botvinick & Cohen 1998) in which the participants control the movements of the index finger of a model hand, in full view, by moving their own finger (hidden from their view) (Kalckert & Ehrsson 2012). In the original paradigm (classical RHI), a fake rubber hand is placed in front of a participant, in full view, whilst the participant's own hand is hidden from her/his

view. The experimenter uses two brushes in order to simultaneously stroke participant's hand and the rubber one. After a few minutes, most of the participants start to experience the touch as originating from the viewed brush (shift in perceived hand location), as if the rubber hand was their own hand (feeling of ownership). Asynchronous stimulation and implausible spatial location of the model hand reduce significantly the illusion (Botvinick & Cohen 1998). This suggests this illusion builds on visuo-tactile integration as well as temporal and spatial congruency of the stimulation. Interestingly, schizophrenia patients tend to experience the RHI faster and stronger than controls, in line with the idea of a more flexible body representation and weakened sense of the self (Peled et al. 2000; Thakkar et al. 2011). Similar results were also reported in psychosis-prone individuals (Germine et al. 2013).

As mentioned previously, self-recognition and bodily awareness rely on a combination between the sense of ownership and the feeling of agency. Considering the classical RHI only tackles the sense of body ownership, the ecological validity of this paradigm is limited. Moreover, since classical RHI does not tap on agency it cannot study the phenomenon of over-inclusive agency experience observed in schizophrenia when viewing a moving hand (Franck et al. 2001; Daprati et al. 1997). The active RHI paradigm, on the other hand, offers the possibility to generate active movements, thus adding the sense of agency to body ownership (Kalckert & Ehrsson 2012; Kalckert & Ehrsson 2014). We ran this paradigm on 71 participants (mean age=24.3 years, range 18–42; 30 males) who were also asked to complete the PDI-21 questionnaire in order to assess their delusion-proneness (mean=6.568, SD=3.42).

In this paradigm, the setup is somewhat similar to the classical RHI; a life-size wooden hand is placed in full view on a box in front of the participant whose own hand is hidden from view, in the box below the model hand (Figure 7). Both hands are wearing a white latex glove, and an opaque cloth is covering the participant's arm as well as part of the fake hand. From the participant's perspective, it looks like she/he is looking at her/his own hand. The active RHI does not involve paintbrush striking, but finger movements. A mechanical coupling device placed between the model hand's index finger and the participant's own index finger, allows the participant to actively move the wooden finger (active condition). It also makes it possible for the experimenter to move both the model hand's and the participant's finger, while the participant is instructed to

remain still (passive condition) – thereby excluding (or minimizing) the involvement of motor intention and efference copy. The connecting stick apparatus also allows creating a time delay between the participant's movements and the wooden finger, allowing synchronous or asynchronous movements, leading to four different conditions: active synchronous, active asynchronous, passive synchronous, passive asynchronous.

Each trial consisted of a 2-minute session during which participants were either performing tapping movements with their index finger (active synchronous or active asynchronous) or were passively experiencing movements generated by the experimenter (passive synchronous or passive asynchronous). The four conditions were randomised and counterbalanced across participants. After each trial participants rated their feeling of ownership over the model hand and agency on the finger movements (four ratings each), using a 7-point Likert scale ranging from "-3" (totally disagree) to "+3" (totally agree) and with 0 signalling uncertainty.

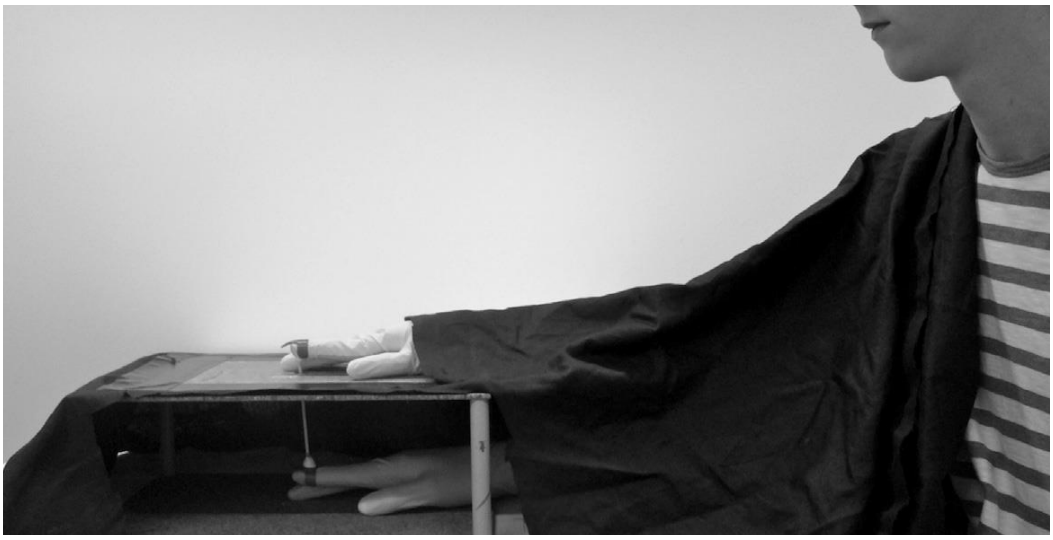

Figure 7. Setup of the moving rubber hand paradigm – a life-size model wooden model hand was placed on a small table/box while the participant's hand lied underneath, hidden from the participant's view. Both hands were wearing the same white latex glove, and an opaque cloth was covering the participant's arm as well as part of the fake hand. This created the impression that the wooden hand the participant was seeing was his/her own. A connecting stick placed between the model hand's index finger and the participant's own index finger, allowed the participant to move actively the wooden finger (active condition). It also allowed the experimenter to move both the model hand and the participant's finger, while the participant was instructed to remain still (passive condition). Reprinted from *When Passive Feels Active - Delusion-Proneness Alters Self-Recognition in the Moving Rubber Hand Illusion.* Louzolo et al. PLOS ONE. 2015. 10(6).

c. Choice Blindness

Choice blindness relies on the manipulation of choices a participant was asked to make. We suggest that this paradigm is predominantly associated with low/intermediate-end of the processing hierarchy, as the priors are generated under a short time during the choice phase (with a duration of a few seconds), preventing them from being processed at a high-level. In the original paradigm, the experimenter is sitting in front of the participants, while holding two pictures in her/his hands. The participant is asked to point at the picture she/he prefers. Then the experimenter puts back both picture cards, moves them toward the participant and turns up the selected card while the other one remains turned down. The participant is required to explain orally why she/he chose that specific picture. Due to a visual trick, the picture that reappears is the one that was not selected in some trials. Participants are not informed about the possibility of manipulations. Choice blindness refers to the instances when the participant does not notice a picture manipulation and confabulates on the reasons behind her/his preference.

In ***Study III***, we used a computerised version of the paradigm. In the original paradigm participants interact with the experimenter and can directly report to him/her when a picture is not the right one. This was not the possible in our study. Instead, we had to measure the detection rate at the time of each trial, without verbal report. In order to do so, we constructed a preference scale that was split into two halves: a negative and a positive part. This allowed participants to rate how much more they liked the picture that reappeared. The left anchor stated “a lot less”, the middle one “neutral” and the right anch or “a lot more”. A negative rating was counted as a detected trial. To make sure participants understood they had to use the left scale in case of a manipulation, they were instructed that if, they clicked too quickly or simply changed their mind, and thus the picture they saw was no longer the one they preferred, they had to indicate this by using the left scale (i.e. between “a lot less” and “neutral” anchors). In addition, they were instructed that, although they had to do their best to use the whole positive scale, if they were not really sure how much more they preferred the picture they selected, they should click somewhere close to the “neutral” anchor on the right half of the rating scale.

d. Instructed fear learning

1. Paradigm and apparatus

The instructed fear learning paradigm was designed in order to study the influence of consciously perceived written instructions (high-order input) on bottom-up low-level learning. The design can be summarised as a classical delay fear conditioning paradigm preceded by an instruction phase.

The principle of classical delay fear condition lies in the repeated pairing of a conditioned stimulus (CS; a stimulus that does not trigger any response initially, e.g. a neutral picture) and an unconditioned stimulus (UCS; a stimulus that in itself triggers a fear response, e.g. a mild electrical stimulation). The UCS usually co-terminates the CS presentation. After several repetitions of this pairing, the UCS is no longer needed to induce the fear response (assessed by ratings or autonomic responses). The subject has learned that the CS predicts the UCS, and the presentation of the CS only is enough to trigger a fear (Knight 2004).

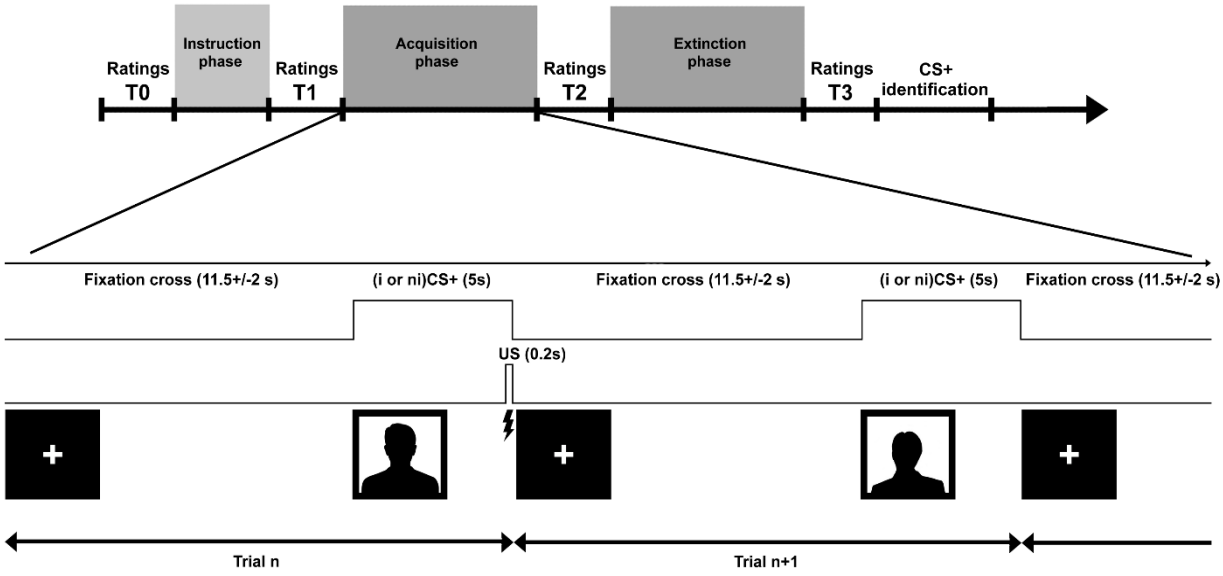

Figure 8. Timeline for the instructed fear learning paradigm. The paradigm started with an instruction phase, followed by a fear acquisition phase, and ended with an extinction phase. In acquisition and extinction phases each CS was displayed 12 times for 5 sec, in a pseudo-randomised order. The jittered inter-trial interval was 11.5± 2 sec. In acquisition phase both instructed and non-instructed CS+ were coupled with UCS (electrical stimulation) with a 50% contingency. There was no UCS in the extinction phase. Before and after each of the three phases participants had to perform likability ratings referred to as T0 (baseline ratings, i.e. before instructions), T1 (after instructions), T2 (after acquisition) and T3 (after extinction). Following the last rating (T3) participants were shown the four CS and asked to click on the two that gave them shocks.

In our study, CS consisted of four Caucasian males with a neutral facial expression: 2 CS+ and 2 CS-, randomised across participants. We used mild electric stimulation on the left forearm as UCS. The intensity of the stimulation was set by the participant during a standard workup procedure. The paradigm comprised an instruction phase, followed by a fear acquisition phase, and then an extinction phase (Figure 8).

In the instruction phase two of the faces (instructed CS+ and CS-; iCS+/iCS-) were presented together with a fabricated short written description about their personality

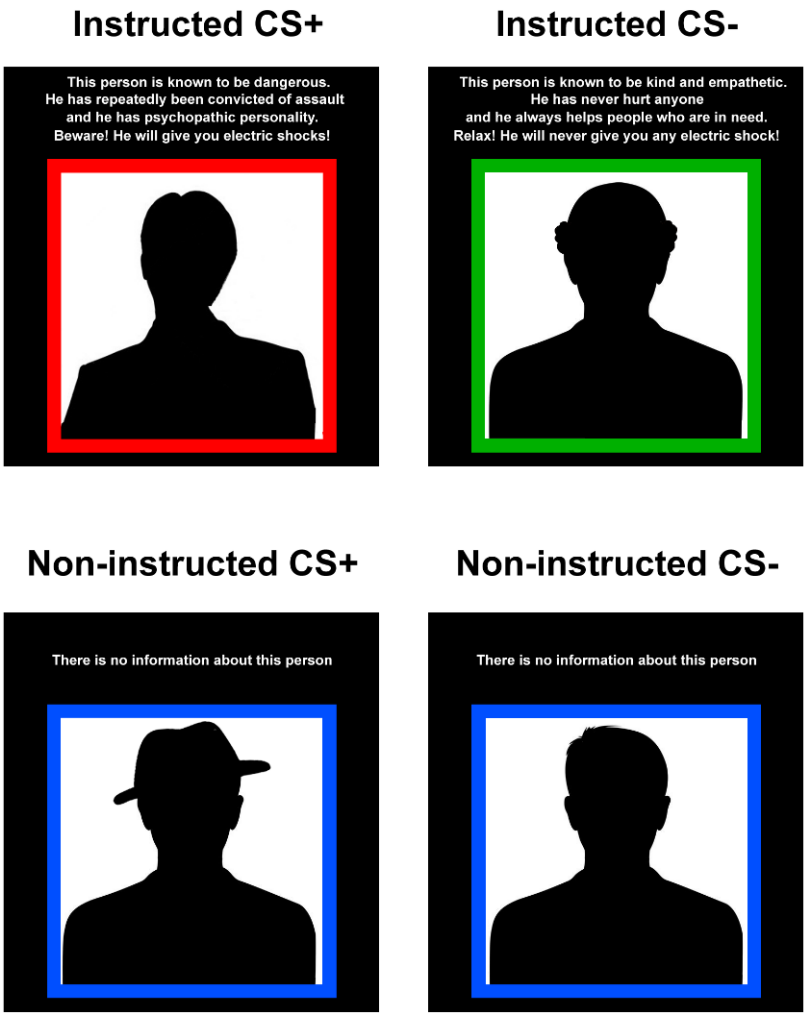

Figure 9. Schema of the 4 CS during the instruction phase. In instruction phase, two of the faces (iCS+/iCS-) were presented together with information about their UCS contingencies that included a fabricated short description (in Swedish in the experiment) about their personality and the risk of being associated with a "shock". The two other CS faces (non-instructed CS+/CS-; niCS+/niCS-) contained no information about their contingencies with the UCS. Instructions were presented twice (followed by ratings) in order to increase the effect of information. After both presentations participants were asked to select which picture would give them shocks (iCS+) and which one would never do (iCS-). This was used both to make sure they understood and integrated the instructions, and to reinforce their expectations regarding the contingencies.

and the risk of being associated with a "shock" (Figure 9). The two other CS faces (non-instructed CS+ and CS-; niCS+/niCS-) were presented without any information about their UCS contingencies. In the acquisition phase, each CS was shown 12 times for 5 seconds, and the jittered inter-trial interval was set to 11.5± 2 seconds. Fifty percent of the CS+ presentations were co-terminated with the UCS (50% contingency). The presentation order was pseudo-randomised to avoid the presentation of two reinforced trials in a row. The extinction phase followed the same procedure, except that no CS+ presentation was reinforced.

2. Behavioural response

Explicit response – likability ratings

Explicit fear learning was assessed with likability ratings, as in evaluative fear conditioning (Petrovic et al. 2008). We argue that explicit ratings mirror a semantic higher order processing of information and therefore represent higher order priors. Before and after each phase of the paradigm, participants were asked to rate with a visual analogue scale, how friendly they thought each CS-face appeared (left anchor stated "the least sympathetic person you can imagine", and the right anchor stated "the most sympathetic person you can imagine" in Swedish). During the debriefing session following the experiment, participants were also asked to rate from 0 to 10 how much they felt they had been influenced by the instructions, and by the "shocks", respectively.

Implicit response – skin conductance response (SCR)

In addition to the explicit conditioning response, skin conductance was also recorded during the acquisition and extinction phases as an implicit online measure of fear conditioning. Electrodermal activity recording is used as a measure of emotional states since skin resistance varies with the activity of eccrine sweat glands that are associated with an emotional stress response (Dawson et al. 2007; Boucsein 2012). Eccrine sweat glands are specific sweat glands found on the whole body but with the highest concentration in palms and soles. Their primary role is thermoregulation; however, it is unclear whether the glands specifically located on palmar or plantar sites are actually involved in evaporation cooling. Instead they seem to be rather related to response to psychologically relevant stimuli (Dawson et al. 2007; Boucsein 2012). Eccrine sweat glands are controlled by the sympathetic nervous system; when the sympathetic

nervous system is activated (e.g. when a fearful stimulus is presented) these glands release sweat that then rises along the cells' tubular duct, to be excreted on the skin surface. As sweat accumulates in the duct, the water and electrolytes it contains increase electrical conductivity. The amplitude of the conductance increase is proportional to the sympathetic arousal, and although small, the response can be recorded by placing two recording electrodes on the skin (in ***Study IV*** electrodes were attached to the distal phalange of the first and third fingers of participants' left hand). Thus the amplitude of the conductance change can be used as an indication of emotional and sympathetic responses (Lang et al. 1990; Boucsein 2012; Dawson et al. 2007).

Unfortunately, SCR is not always a reliable measure due to diverse reasons, and some people fail to display this signal when presented with relevant stimuli. In addition, when acquired in an fMRI scanner the data is often noisy. Here we only used SCR data from the so-called responders, namely participants who displayed a SCR to at least 20% of the presentations of each CS. Nevertheless, many of them were characterised by a low reactivity, meaning that they did not respond to much more than this 20%-threshold. Thus, the poor quality of our SCR data limited the number of analyses that could be performed using this variable.

e. Functional Magnetic Resonance Imaging (fMRI)

1. Data acquisition

In order to understand the neuronal underpinnings of our behavioural results in **Study IV** we simultaneously measured the brain activity using functional magnetic resonance imaging (fMRI). fMRI is a non-invasive brain imaging technique that allows an indirect measurement of brain activity, based on a phenomenon called the blood oxygenation level dependent (BOLD) effect (Buxton 2009).

Like any other organ, the brain depends on oxygen to function. While the brain only represents 2% of the body weight, its oxygen needs take up to 20% of the total oxygen consumption (Raichle & Gusnard 2002). Oxygen is delivered to the different organs via blood circulation. More precisely, the red blood cells contain an oxygen-carrying molecule called haemoglobin. Haemoglobin consists of four subunits, each of them

containing one iron ion in its centre (Hardison 1996). Iron is the component that actually binds to oxygen. Oxygen-bound haemoglobin is referred to as oxyhaemoglobin (oxyHb). When it loses oxygen (deoxyhaemoglobin - deoxyHb) its magnetic properties change; it becomes paramagnetic, and thus, decreases MR (magnetic resonance) signal. When a brain area is active, glucose metabolism, oxygen metabolism, blood flow and blood volume increase locally. However, upon increased activity (increased consumption of oxygen by the cells) the $\frac{oxyHb}{deoxyHb}$ ratio increases. The reason behind this seemingly paradox is the fact that upon neural activity the increase in blood flow is much larger than the oxygen metabolic rate (Buxton 2009) (Figure 10). Since OxyHb is less paramagnetic than deoxyHb, an increase in the $\frac{oxyHb}{deoxyHb}$ ratio leads to a local increase in MR signal. The amplitude of this signal change, which is measured by fMRI, is related to the magnitude of the blood flow change (Buxton 2009). Thus, this technique does not measure brain activity *per se*. Instead, it captures changes in blood flow and oxygen metabolism (i.e. the BOLD signal), and from these, infers brain activity. It should be kept in mind that the metabolic change in blood oxygenation detected by fMRI is not immediate. It follows the stimulus presentation onset with a delay of about 6 seconds. This time lag has to be taken into account when modelling the BOLD signal change in relation to stimulus presentations (Buxton 2009; Liao et al. 2002). This means the BOLD response will have a width of about 3 sec (for short stimulus presentation) and its peak will be at about 5-6 seconds after the stimulus onset. Due to this time delay, the temporal resolution achieved by fMRI is quite low (Glover 2011). One of its strengths on the other hand, is its good spatial resolution (3-4 mm in most applications) (Glover 2011).

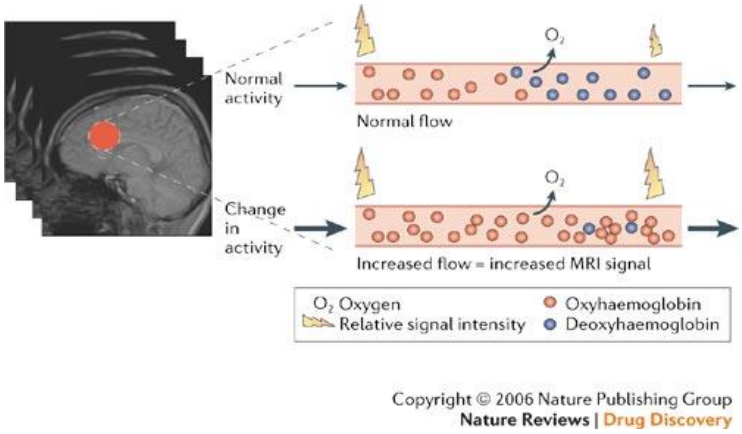

Figure 10. Change in oxyHb/deoxyHb ratio during increased neural activity. *Reprinted by permission from Macmillan Publishers Ltd: Nature Reviews Drug Discovery, Borsook et al, copyright 2006*

In our study, participants performed the instructed learning paradigm while lying down

in a 3T MR General Electric scanner, with a 32-channel head coil. A T1-weighted structural image was acquired before the paradigm started. Functional scans were obtained using a gradient echo sequence T2*-weighted echo-planar imaging scan (TR=2.334 sec, TE=30 ms, flip angle=90 degrees, 49 axial slices in ascending order (thickness=3 mm) and a field of view (FOV)=22cm, matrix size=72x72x3mm). The first four scans were defined as dummy scans and discarded from the analysis. Functional image acquisition comprised two sessions of 245 volumes each that corresponded to the acquisition phase and the extinction phases in the conditioning paradigm. There was a break of approximately 4-5 minutes between the two sessions during which participants completed likability ratings (T2).

2. Data analysis

For each participant the data were pre-processed and analysed using the default pipeline of SPM8 software package (Statistical parametric mapping, Welcome Department of Cognitive Neurology, London, UK http://www.fil.ion.ucl.ac.uk/spm). For more detail, see Methods in ***Study IV***.

For the first-level analyses, a general linear model (GLM) with one regressor per CS type (iCS+, iCS−, niCS+ and niCS−) - each onset modelled as a 5-second event - and one regressor for the UCS presentation. In addition, the four CS regressors were also parametrically modulated with a linearly changing function to capture activity changes over time. This resulted in a total of 9 regressors that were convolved with the canonical hemodynamic response function and entered into the GLM as implemented in SPM. Motion regressors were also included in the model. The acquisition and the extinction phases were modelled and analysed separately.

In a second level analysis we studied the main effects of 1) conditioning (CS+ versus CS-), 2) instructions (instructed CS versus non-instructed CS), and 3) pain for all subjects together. When studying group differences between delusion-prone and controls on these activations we used a region of interest (ROI) approach in order to increase the sensitivity. For the main effect of instructions, we applied small-volume correction (SVC) for multiple comparisons within an anatomical lOfc ROI (defined using SPM pick atlas) as our primary hypothesis was targeting the lOfc. The remaining ROIs

consisted of spheres (6mm radius) centred on the maximally activated voxels in caudal ACC (cACC) and anterior insula for the conditioning effect, and on posterior insula for the effect of pain. All our results were assessed at $p<0.05$, family-wise error (FWE) corrected for multiple comparisons.

In addition to studying activation patterns, we also examined functional connectivity using a psychophysiological interaction (PPI) analysis in SPM. This type of analyses allows the identification of context-induced changes in the strength of connectivity between brain regions. We assessed connectivity changes between the right lOfc and the rest of the brain based on the previously reported involved of right lOfc in placebo and emotional reappraisal appraisal (Petrovic et al. 2005; Petrovic et al. 2010; Wager et al. 2008). In order to do so we used a sphere with a radius of 6 mm centred on the peak activation in the right lOfc region in the instruction contrast (GLM analyses). Two contrasts were used for the PPI analyses as the physiological factor: the general effects of instruction (iCS vs niCS) and the instruction effect on conditioning (i(CS+ vs CS-) versus ni(CS+ vs CS-). Our results were again assessed at $p<0.05$, FWE corrected for multiple comparisons.

VI – Summary of the results

a. Study I

In ***Study I*** we manipulated the experience of ownership and agency in delusion-prone individuals in order to try to understand whether hypersalience, or a faulty low-level prediction system (characterised by imprecise priors), could explain self-recognition impairments observed in psychosis-related states. Our results point towards the involvement of both mechanisms in delusion-proneness.

As mentioned previously, the main difference between active and passive conditions is the presence of intentions and motor predictions (including efference copy) in the first condition. Thus, if low-level predictions were the only dysfunctional system (in terms of imprecise priors), only the active condition would be showing a difference related to delusion-proneness. On the other hand, if the hypersalience hypothesis was the source of the impairment, then both the active and the passive conditions would show increased self-recognition (exacerbation of the illusion, and aberrant over-inclusive agency, respectively), due to an increased integration of incoming signals.

Overall, our results revealed that delusion-proneness was associated with aberrant self-recognition in line with previous work reporting more flexible body representations in psychosis-related states (Thakkar et al. 2011; Peled et al. 2000). More specifically, all participants reported similar levels of agency feeling over the model hand independent of their degree of delusion-proneness ($r=-0.111$, $p=0.358$). Interestingly, in the passive condition – a condition under which the feeling of agency is normally abolished (Kalckert & Ehrsson 2012) – delusion-prone individuals experienced levels of agency related to the rubber hand that were similar to the ones they reported during the active condition (Figure 11). The over-inclusive agency phenomenon observed in the passive condition suggests that delusion-prone individuals tended to experience externally-generated movements as self-produced produced, in line with previous work (Daprati et al. 1997; Franck et al. 2001). The result implies that in the absence of motor predictions and intentions, delusion-prone individuals construct an abnormal feeling of agency based solely on the aberrant (hyper) integration of incoming signals integration of incoming signals. This

observation together with the general increase of ownership feeling with delusion-proneness, support the hypersalience hypothesis in psychosis-related states. In the active condition, hypersalience of external input would exacerbate the normal feeling of agency. However, our data suggests that in case of experience of agency in the active condition, the hypersalience bias would actually compensate the lack of reliable motor predictions (including imprecise priors). The experience of agency would thus seemingly be close to normal but instead of relying on the motor prediction system, it would be driven by an increased integration of external input.

In summary ***Study I*** brings supporting evidence to the hypothesis of an impaired low-level prediction system co-existing with a hypersalience bias.

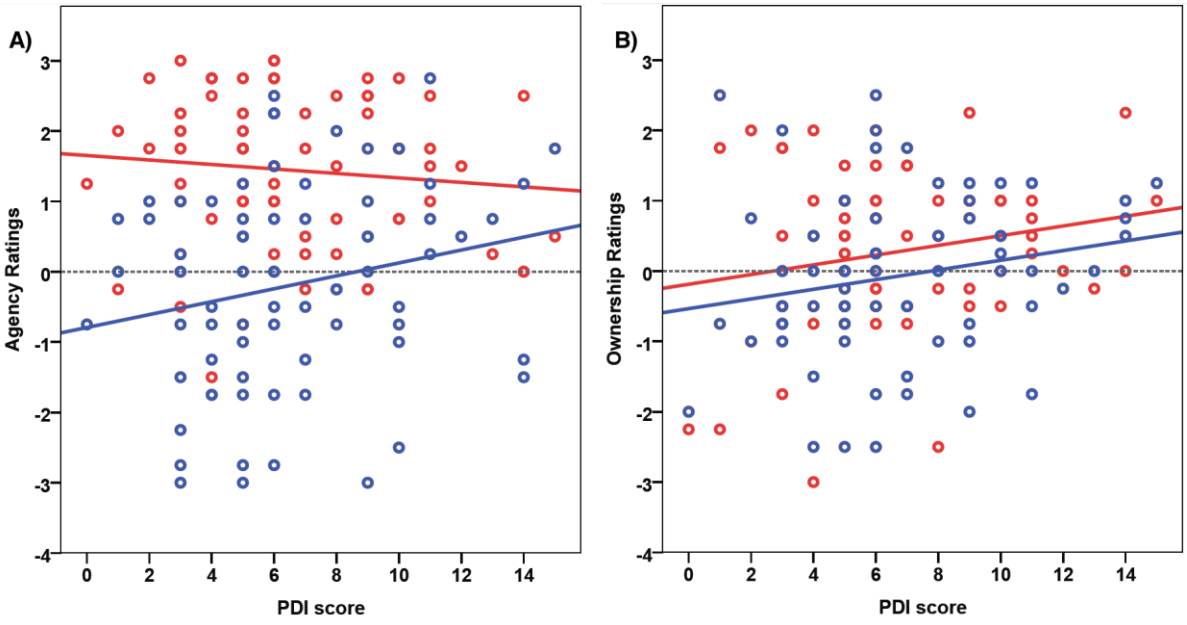

Figure 11. Correlations between PDI score and agency (**A**), and ownership (**B**) ratings, in active (red) and passive (blue) conditions. **A**. Active conditions r=-0.111, p=0.358, Passive conditions r=0.232*, p=0.05; **B**. Active conditions r=0.177, p=0.139 Passive conditions r=0.259*, p= 0.029. Reprinted from *When Passive Feels Active - Delusion-Proneness Alters Self-Recognition in the Moving Rubber Hand Illusion.* Louzolo et al. PLOS ONE. 2015. 10(6).

b. Study II

In ***Study II*** we examined the relation between delusion-proneness and ADHD/ASD tendencies, and investigated which particular dimensions were the most closely related

to psychosis. Our results revealed a weak positive correlation with ASD tendency (r=0.192, p<0.001) and a moderate positive correlation with the ADHD trait (r=0.406, p<0.001) (Figure 12), and is thus confirming previous work pointing towards overlaps between psychotic disorders and ADHD/ASD (Dalsgaard et al. 2014; Stahlberg et al. 2004; Larsson et al. 2013; Chisholm et al. 2015). However, our study extends these finding to the associated traits. Similar correlations were found when analyses were conducted on the items that had been described as prototypical to the disorder they were assessing (PDI/AQ correlation r=0.129, p<0.001; PDI/ASRS correlation r=0.324, p<0.001) (Figure 12).

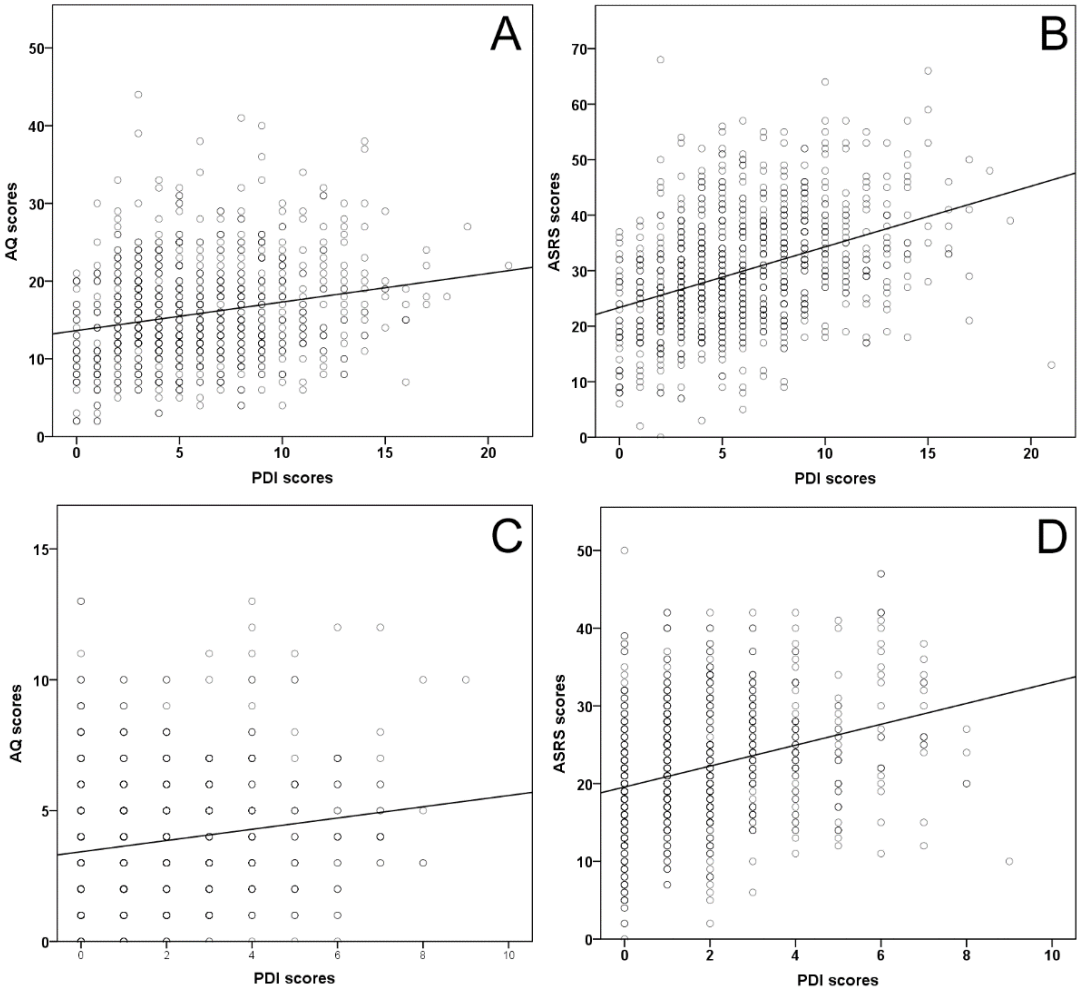

Figure 12. Correlations between PDI scores and AQ/ASRS scores on full (A and B) and truncated (C and D) versions of the questionnaires.
A: Correlation between PDI scores and AQ scores – r = 0.192**
B: Correlation between PDI scores and ASRS scores – r = 0.406**
C: Correlation between PDI scores and AQ scores – r = 0.129**
D: Correlation between PDI scores and ASRS scores – r = 0.324**
*** p<.001 two-tailed Spearman's correlations*
Reprinted from *Delusion-proneness displays comorbidity with traits of autistic-spectrum disorders and ADHD.* Louzolo et al. PLOS ONE. 2017. 12(5).

In a second step we furthered the investigation in order to identify which particular ADHD/ASD dimensions were more related to psychosis tendencies by applying a factor analysis on our dataset. Our results revealed that the delusion-proneness factor correlated strongly with three ADHD factors (impulsivity, inattention, hyperactivity), and to a lesser with an ASD factors.

Altogether, our results support the idea of the existence of subclinical symptoms, shared by psychosis-proneness and ASD- or ADHD-traits, in particular related to hyperactivity/impulsivity and communication. Our results do not allow drawing any conclusion in terms of causal relationship, or on whether these co-morbidities reflect shared underlying mechanisms. However, the idea of general shared mechanisms underlying different psychiatric disorders has been discussed extensively the last years (Caspi et al. 2014; Lahey et al. 2012) and it is possible that it may be mirrored in the relation between different subclinical traits.

c. Study III

In line with our hypothesis, ***Study III*** showed that delusion-prone individuals were more likely than controls to accept false feedback and display confabulation-associated behaviour when facing perceptual ambiguity.

Overall, delusion-prone participants failed more often than controls to detect picture manipulations (t=2.088, df=40.351, p=0.021 one-tailed independent sample t-test on average detection rates) (Figure 13). In addition, they gave significantly more extreme preference ratings to those non-detected trials, than controls did (average rating delusion-prone group=35.20, SD=18.18; average rating control group=23.06, SD=10.77; independent sample t-test t=-2.959, df=48, p=0.005). This could not be explained by a general tendency to give more extreme ratings as there was no group difference on baseline ratings. Instead, this points towards a tendency of delusion-prone individuals to be over-confident in the way they appraise their own preferences or performance. These observations mimic previous work on psychosis-related states repeatedly showing larger propensity to experience false recognition or bias against disconfirmatory evidence and to be overly confident in them (Joyce et al. 2013).

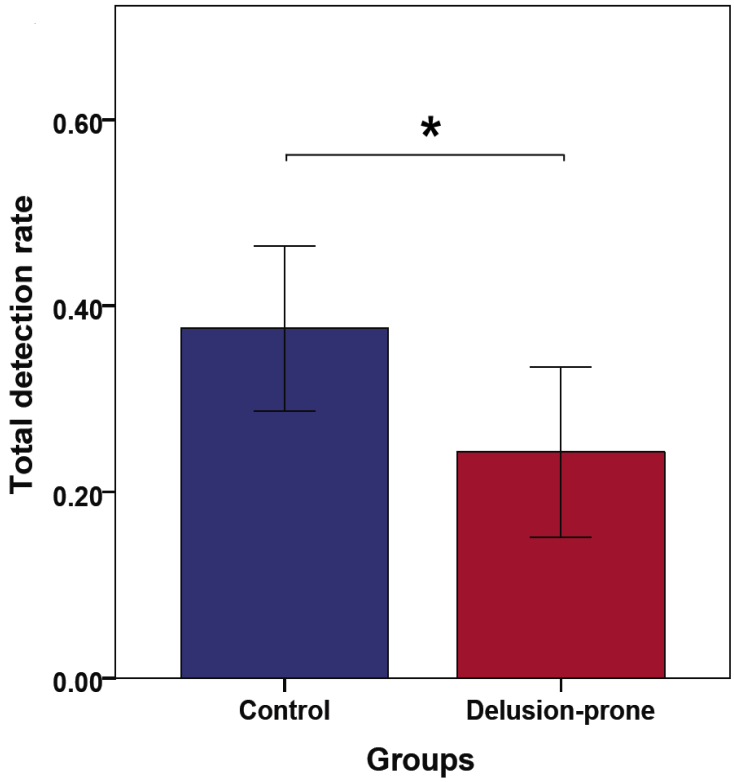

Figure 13. Detection rates. Overall detection rate in the control group (mean=0.38, SD=0.26) and delusion-prone group (mean=0.24, SD=0.18). The group difference was significant (t=2.088, df=40.351, p=0.021 one-tailed).

Interestingly, the difference between delusion-prone participants' preference ratings on non-detected manipulations and detected/non-manipulated trials was comparable to the equivalent difference in control participants (Figure 14). Preference ratings on non-detected manipulations compared to detected (absolute values) or non-manipulated preference ratings can be viewed as a proxy to subconscious uncertainty in the face of perceptual ambiguity. The smaller the non-detected ratings are (as compared to the two other preference ratings), the more uncertain the participant is. Our results thus suggest that while delusion-prone individuals were more impaired in conscious error detection, at the subconscious level they seemed to experience a degree of uncertainty when facing ambiguous stimuli that was similar to controls.

Finally, we also observed a time effect on detection rates that was similar in both groups. Namely, all participants improved their detection rate with time (time effect $F(1,48)=62.687$, $p<0.001$ – (time x group) repeated-measure general linear model).

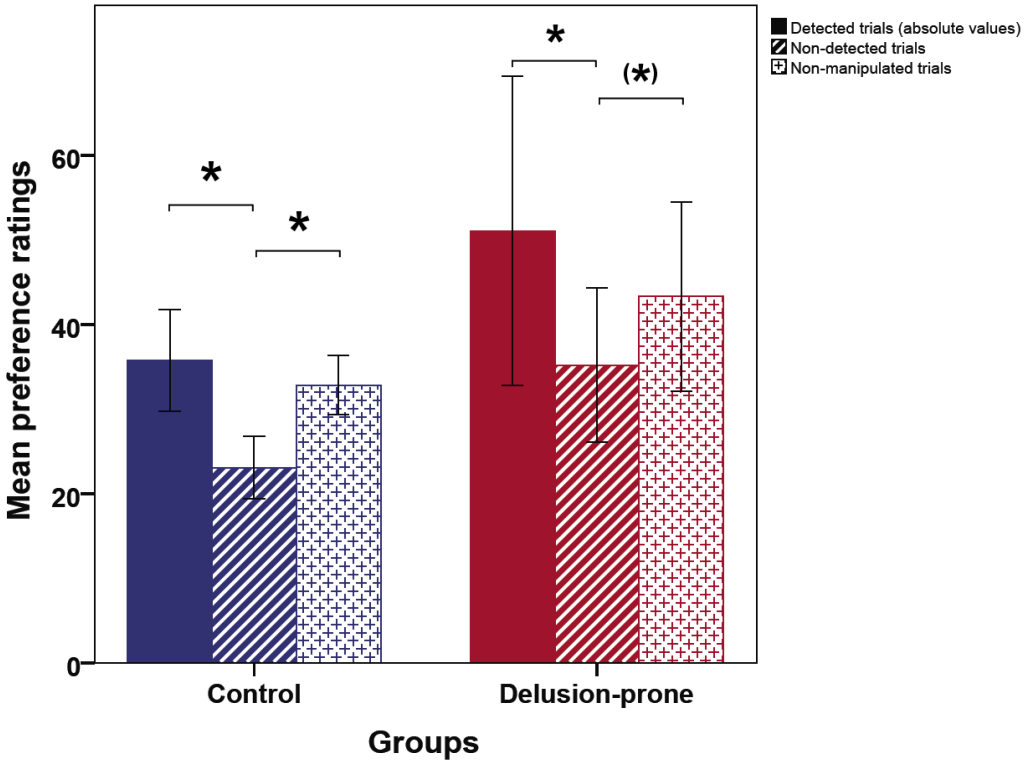

Figure 14. Mean preference ratings on detected trials, non-detected manipulations and non-manipulated trials. In the control group, non-detected trials were rated significantly lower than detected trials (absolute value; paired t-test t=4.306, df=33, p<0.001) and non-manipulated trials (paired t-test t=6.758, df=33, p<0.001). In the delusion-prone group, non-detected trials were also rated significantly lower than detected-trials (absolute value; paired t-test t=2.248, df=12, p=0.044) and this difference was on the border of significance in case of non-manipulated trials (paired t-test t=2.066, df=15, p=0.057). There was no group interaction when comparing non-detected trials and detected manipulations (repeated-measure model F=19.485, df=45, p=0.702) or non-detected trials and non-manipulated trials (repeated-measure model F=27.637, df=48, p=0.628)

d. Study IV

Our main hypothesis, stating that instructions would have a larger effect on delusion-prone participants than on controls, was confirmed by our results showing a significantly larger general effect of instructions on fear index scores in the delusion-prone group (t=-2.081, df=41, p=0.022, one-tailed) (Figure 15 B). This result brings supporting evidence to the idea that delusion-proneness is associated with a larger top-down influence of high-order beliefs. Interestingly, when explicitly asked to rate to what extent they felt they have been influenced by the written instructions, delusion-prone participants also reported a higher influence level. When the same question was

asked regarding the influence of shocks, no group difference was observed. This, too, advocates for a larger effect of explicit high-order signals. Moreover, in the delusion-prone group, both implicit and explicit ratings of the effects of instructions (index scores and explicit ratings, respectively) correlated positively with distress. This speaks towards a relation between the level of distress associated with delusions and the top-down influence of high-order beliefs. This observation is especially interesting in light of studies that identified distress as the main factor differentiating psychosis-prone individuals from clinical populations, in terms of delusional ideation (Peters, Day, et al. 1999; Lim et al. 2011; Lim et al. 2014; Cella et al. 2012). Our results thus add to the body of evidence stressing the importance of distress in delusion-proneness, and arguing for taking this dimension into greater account when studying psychosis-related states.

During extinction, repeated exposures to CS+ without any UCS pairing gradually eliminate the physiological fear response (Sehlmeyer et al. 2009). However when it comes to evaluative conditioning, a resistance to extinction is commonly reported (Gawronski et al. 2015). In line with this, both groups showed resistance to extinction in the context of the instructed CS. Interestingly, while the control group displayed a trend towards an extinction effect ($t=1.63$, $df=22$, $p=0.059$, one-tailed paired t-test), fear learning (represented by fear index scores) seemed to increase after extinction in the delusion-prone group ($t=-1.78$ $p=0.09$ two-tailed, paired t-test) yielding a significant interaction ($t=2.339$, $df=41$, $p=0.024$). In other words, instead of becoming more neutral in their judgement regarding the faces, delusion-prone individuals turned even more extreme in their ratings (Figure 15).

In terms of brain activity, fear conditioning led to activation in brain areas commonly reported in conditioning in both groups (Fullana et al. 2015). In line with our hypothesis, instructions activated the lOfc (Figure 16). Although this activation pattern was mainly driven by delusion-prone subjects (that was the only group showing a significant bilateral activation in lOfc bilaterally), there was no significant group difference. When studying functional connectivity associated with the general effect of instructions, the PPI analysis revealed increased connectivity between right lOfc and right posterior insula ($Z=3.29$, corrected $p=0.004$) specifically in delusion-prone individuals. Posterior insula is considered one of the primary nociceptive input regions. Thus the increased association observed between this region and lOfc in the instruction

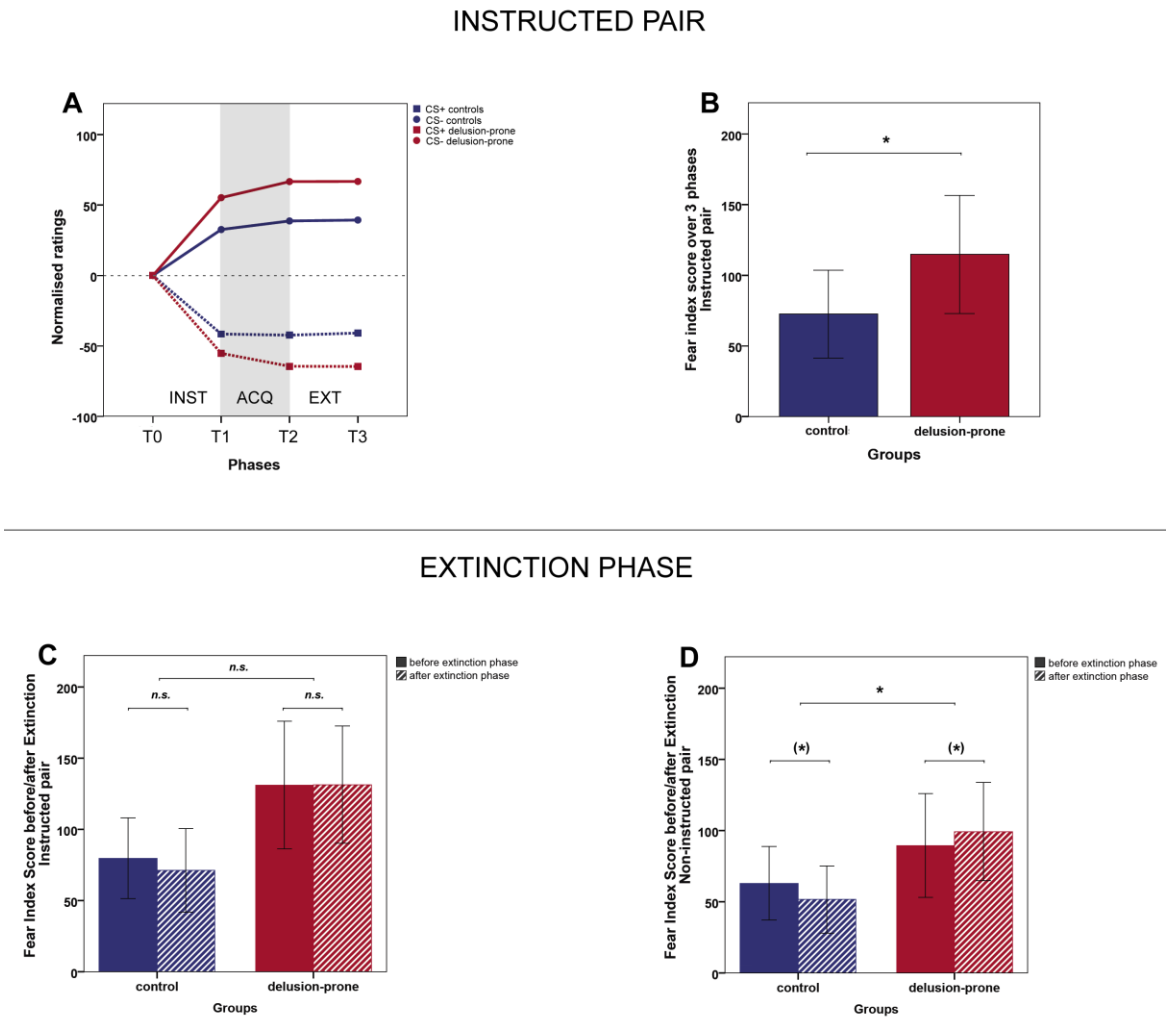

Figure 15. Explicit behavioural responses to instructed learning. (A) Timeline of likability ratings for instructed CS after instructions, acquisition and extinction phases. **(B)** Overall instructed fear index scores (averaged over 3 phases) are significantly larger in the delusion-prone group (mean=125.77, SD=93.06) than in the control group (mean=74.50, SD=67.98 – independent-sample t-test t=-2.081, df=41, p=0.022, one-tailed). **(C)** No extinction effect for the instructed stimuli when comparing fear index scores before and after the extinction phase (T2 and T3) for any of the groups (delusion-prone group: t=-0.048, df=19, p=0.96, paired t-test; control group: t=1.04, df=22, p=0.31, paired t-test) nor any group x phase interaction (t=0.872, df=41, p=0.388). **(D)** Significant interaction between the groups on the extinction effect for the non-instructed stimulus pairs (t=2.339, df=41, p=0.024). While the control group tended to show a significant extinction (t=1.63, df=22, p=0.059 one-tailed paired t-test), the delusion-prone group tended to show an opposite effect, i.e. increased fear index score after extinction (t=-1.78 p=0.09), when the two groups were examined separately. INST: instruction phase, ACQ: acquisition phase, EXT: extinction phase, T0 to T3 see Figure 8

contrasts mirrors the previously reported increased influence of intermediate/high-level priors in lObc on sensory processing in delusion-prone individuals (Schmack et al. 2013). Moreover, the PPI analysis suggested that the connectivity between lOfc and cACC was significantly increased in delusion-prone participants compared to controls,

when investigating how instructions specifically influenced fear conditioning (Z=2.96, corrected p=0.012).

Our results revealed a group differences in terms of functional connectivity between lOfc and pain/fear processing areas, and not in activation levels. This implies that, in delusion-prone individuals, high-level priors do not necessarily lead to modified activity, but instead, they change the way specific brain regions interact. Our results are in line with previous work suggesting the involvement of lOfc in re-appraisal (Wager et al. 2008) and placebo analgesia (Petrovic et al. 2005; Krummenacher, Candia, et al. 2010; Petrovic et al. 2010). Moreover, research suggests a role for orbito-frontal cortex in top-down facilitation in visual object recognition (Bar 2003). More precisely, orbito-frontal cortex is presented as a potential source of top-down predictions helping speed up object recognition processes (Bar 2003). Finally, and similarly to our results, functional connectivity between lOfc and sensory processing areas was also associated with delusion-proneness, in a conditioned visual illusion paradigm (Schmack et al. 2013).

In summary, our study together with existing literature, bring supporting evidence to a larger top-down influence of high-order beliefs in delusion-proneness. In addition, our result also confirm an involvement of lOfc in the generation of high-order priors, and point towards an increased top-down influence from lOfc on primary sensory areas, associated with delusion-proneness.

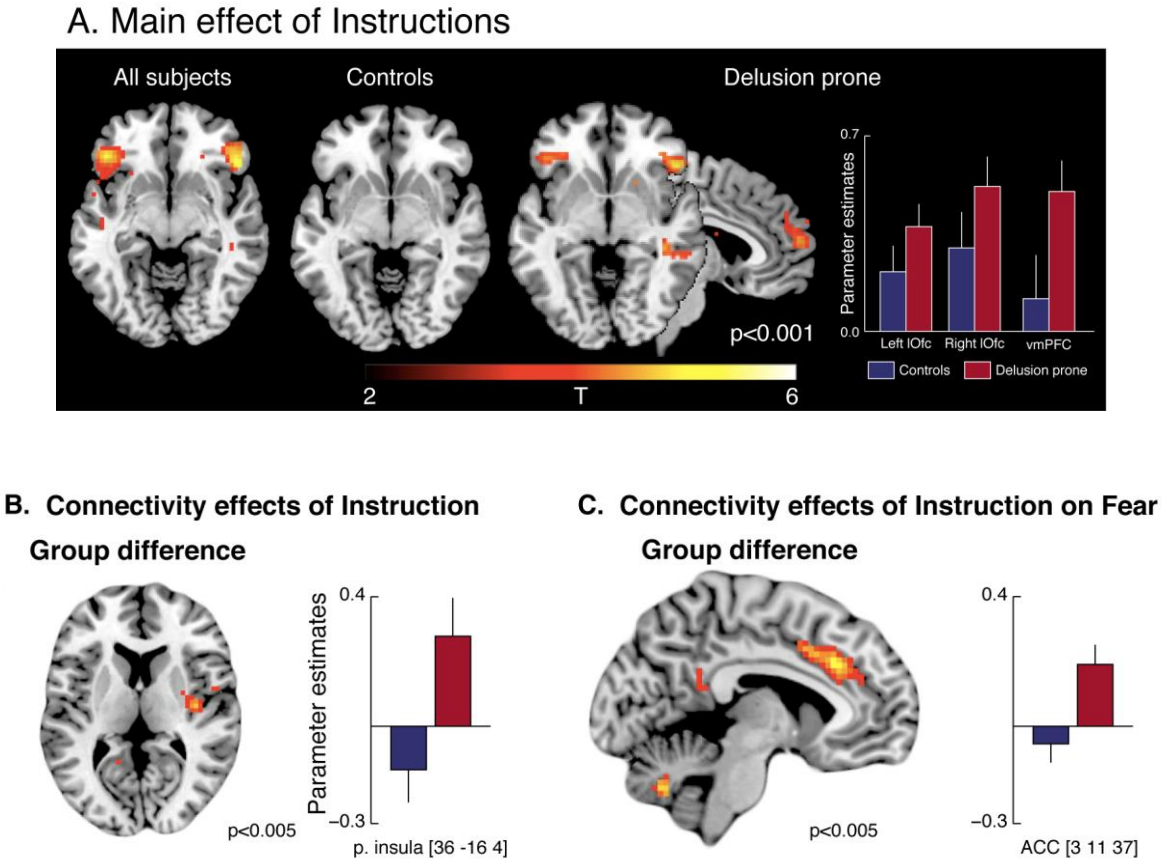

Figure 16. BOLD response (A) and functional connectivity analyses (B & C). (**A**) The main effect of instructions showed a bilateral activation in lOfc, which was mainly driven by the delusion-prone group (there was no tendency of lOfc activation at the present threshold for the control group, while the lOfc activation was highly significant and bilateral for the delusion-prone group). In addition, delusion-prone individuals also displayed activation in vmPFC that was not reported in the control group, nor in the all-subject activations. (**B**) A PPI analysis of the effect of Instructions revealed increased connectivity between right lOfc and functionally defined low-level pain processing areas (i.e. right posterior insula), specifically for delusion-prone individuals (Z = 3.29, corrected p = 0.004). (**C**) A PPI analysis of the effects of instruction on fear processing showed a significantly larger connectivity between lOfc and cACC, overlapping with fear related activation, in delusion-prone than in control participants (Z = 2.96, corrected p = 0.012).

V – Discussion

The work presented in this thesis helps to further the understanding of unusual experiences reported in psychosis-related states. The central picture emerging from our studies, and in line with previous work, is that delusion-proneness is associated with disrupted experiences, ranging from self-recognition to beliefs, as well as an altered decision-making. In psychosis-related states, the experience of the world and of the self is imprecise and fluctuates. From a predictive coding perspective, these impairments have commonly been explained by poor precision and instability of the low-level prediction system. However, as described earlier, this hypothesis is puzzling in light of the phenomenon of delusions (i.e. overly stable high-level beliefs). Our research was thus conceived as an attempt to disentangle the role of low- and high-levels of the processing hierarchy in delusion-proneness, and to reconcile the two sides of this paradox.

a. Low-level prediction systems

Study I and ***III*** were designed to tap onto low and intermediate levels of the processing hierarchy, with paradigms that pertained to different cognitive domains, in order to be representative of a few of the impairments observed in schizophrenia: ***Study I*** targeted self-recognition, while ***Study III*** targeted decision making and confabulations. Our results confirmed the weak and unstable nature of low-level priors in delusion-prone individuals manifested in a blurred experience of the self and a liberal acceptance bias in this group of subjects.

In a context where low-level priors are based on external input, they have to be built in a bottom-up fashion (Friston 2005). These priors are then used to process new incoming information. However, delusion-prone individuals and psychosis patients fail to create stable low-level priors, possibly due to the aberrant (or hyper-) salience bias, whereby stimuli are wrongly attributed salience (Kapur 2003), which might be related to an over-responsive dopamine system (Weinstein et al. 2017; Abi-Dargham et al. 2004; Woodward et al. 2011; Egerton et al. 2013; Fusar-Poli et al. 2011; Howes et al. 2009). Every time a new incoming signal appears, it generates a prior that overwrites

existing ones, which does not allow constructions of stable priors in these hierarchies. As mentioned earlier, a prime example of this, is altered mismatch negativity displayed by schizophrenia individuals in oddball studies (Javitt et al. 1998; Javitt et al. 1993). Such studies focus on changes in brain activity when a new input appears amidst an otherwise continuous repetitive sequence of a stimulus. While control participants successfully detect the deviant signal thanks to a transient memory trace they acquired about the repeated stimulus that acts as a low-level prior, schizophrenia and at-risk participants fail to create such priors which limits their detection abilities (Javitt et al. 1998; Javitt et al. 1993; Atkinson et al. 2012; Brockhaus-Dumke et al. 2005). Other tasks such as prepulse inhibition (Swerdlow et al. 2006; Javitt & Freedman 2015; Braff et al. 1992) and perceptual stability in the random dot kinetogram (RDK) illusion (Schmack et al. 2013) also suggest weak low-level priors in psychosis related states. We suggest that delusion-prone subjects failed to detect manipulated faces in the choice-blindness paradigm (***Study III***) due to their inability to form an initial reliable prior, combined with a tendency to give new stimuli too much salience, i.e. they regarded the displayed non-chosen face as too salient to dismiss. Importantly, this effect was not due to a difference in general working memory capacity. Thus, the problem is not working memory *per se* but building priors based on new and overly salient input.

Impairments in low-level priors are not limited to external input. Studies on self-induced touch (Blakemore, Wolpert, et al. 2000) and force matching (Shergill et al. 2005) suggest that also internally generated priors are imprecise in psychosis related states. Based on our results from ***Study I*** we argue that since delusion-prone individuals and patients with psychosis also show difficulties to build precise low-level priors when expectations are internally generated (i.e. efference copy), they need to rely on incoming signals in order to build sense of agency. Thus, it may be suggested that the perceptions of psychosis patients and delusion-prone individuals are biased towards the input they receive both in the case of externally generated and internally generated priors.

A way to conceptualise this, is that in the absence of existing higher-level priors or reliable self-generated low-level priors, it seems schizophrenia patients, and to a lesser extent psychosis-prone individuals, perceive the world moment-to-moment, and their experience of the world is actually closer to what the environment is like at a given time,

than in control subjects. This is echoed in findings with the force-matching task (Shergill et al. 2005; Teufel et al. 2010). The suggestion that patients with psychosis and delusion-prone subjects do not take into consideration the temporal history of a situation as much as controls, and mainly focus on the present time, may also relate to the *jumping-to-conclusion bias*. These studies have suggested that schizophrenia patients experience difficulties in incorporating prior evidence in their decision strategy and show a recency effect and hasty decisions (Evans et al. 2015; Garety et al. 1991; Moritz & Woodward 2005; Joyce et al. 2013).

b. High-level prediction system

Contrary to weak low-level priors, the presence of delusions suggests that high-level priors have unusual high precision in psychosis-related states. Two recent studies brought some experimental data supporting this argument (Schmack et al. 2013; Teufel et al. 2015). Those studies used paradigms in which participants had to make sense of ambiguous stimuli. Schmack and colleagues used the RDK paradigm where participants were presented with moving dots on a screen (Schmack et al. 2013). The task was to identify in which direction the dots were moving - which actually is an illusionary effect of the RDK. After being tricked into believing that the googles the experimenter gave them had influence over the motion direction of the dots, participants were tested on moving dots where the experienced direction normally is ambiguous and jumps between left and right. The study suggested that delusion-prone individuals relied extensively on their expectations (i.e. the googles affected the motion direction) to make sense of their ambiguous perceptions, as compared to non-delusion-prone subjects.

In Teufel's study (Teufel et al. 2015), two-tone images that looked like random black and white patches in the absence of appropriate prior information were first presented to participants. After this presentation, the colour templates of the two-tone images depicting natural scenes with people were shown. Finally, the same black and white pictures as initially presented were shown once again. In the two-tone blocks, participants were required to indicate whether a person was present on each picture. Similar to Schmack's study, the hypothesis was that patients and delusion-prone individuals would make a greater use of their prior knowledge (the unambiguous

colour templates) in order to make sense of the two-tone images. Also, this study showed that delusion-prone individuals (and psychosis patients) relied more strongly on top-down signals in order to disambiguate the presented stimuli (Schmack et al. 2013; Teufel et al. 2015).

Study IV confirms and extends these observations by suggesting that stronger top-down influence of beliefs observed in delusion-prone individuals is not limited to sensory perception, but may also apply to complex processes, like evaluative fear learning. In contrast to the two other studies, our design made it also possible to show that delusion-prone participants already had formed more strong beliefs before the reinforcing sensory evidence (i.e. after the presentation of instructions). We argue that this finding extends the idea by Kapur (Kapur 2003), i.e. that overly strong beliefs are formed in order to explain specific aberrant stimuli, to that this effects also may represent a coping strategy in order to better understand a noisy low-level perception.

Our fMRI results from the same study showed an activation of lOfc in the main effect of instructions and a stronger functional connectivity between lOfc and structures processing fear and pain in the delusion-prone group. As lOfc is involved in cognitive reappraisal (Wager et al. 2008; Golkar et al. 2012; Eippert et al. 2007) our findings support the idea that delusion-prone subjects actually use higher order priors to better understand the input as a coping strategy. It has also been suggested that lOfc is a key structure in the placebo effect in which higher-order expectations (or priors) are given to subjects and patients leading to a changed experience of pain or unpleasantness (Petrovic et al. 2002; Petrovic et al. 2005; Petrovic et al. 2010; Wager & Atlas 2015). Additionally, it was also proposed that delusion-proneness was associated with an involvement of lOfc in mediating belief-congruent information in visual processing in the RDK illusion (Schmack et al. 2013). Thus, our data suggest that overly strong beliefs are formed, not only as a direct consequence of understanding specific aberrant input (Kapur 2003), but also as a way to better understand a generally noisy environment using available higher order information.

Our results also mirror the jumping-to-conclusion bias and bias against disconfirmatory evidence that were reported in schizophrenia patients, on a task involving the generation of high-order beliefs (Veckenstedt et al. 2011). In line with this

study, our results suggest that our delusion-prone participants required much less evidence in order to assume a statement was true, update their model of the world accordingly and stick to that view. However, this idea still does not explain why the high-level models are more stable than the low-level models in psychosis-related states.

c. The search for a meaning

As discussed previously, it has been suggested that due to the aberrant salience attribution bias, many signals that should have been ignored become highly relevant (Kapur 2003). This results in experiences that can hardly be explained in a fast, automatic way. Thus, while psychotic and delusion-prone individuals fail to create stable low-level priors, they keep on being bombarded by aberrant input. Accumulation of the resulting unresolved errors may generate a feeling of uncertainty and a need for closure (McKay et al. 2006; Colbert & Peters 2002). It has been further suggested that in order to get rid of this uneasy feeling, more cognitively advanced processes and explicit reasoning strategies are required (Kapur 2003). The brain thus attempts to make sense out of signals that are unrelated and irrelevant to the current situation. As a result, erroneous (high-level) causal inferences are generated (Kapur 2003).

Apart from experimental studies in delusion-prone subjects discussed above (Schmack et al. 2013; Teufel et al. 2015), the urge to explain away sensory signals on a higher and more abstract level, was suggested in studies investigating paranormal beliefs. These studies reported a larger inclination to find meaningful patterns in visual noise in paranormal believers (Brugger et al. 1993; Riekki et al. 2013; Blackmore & Moore 1994; Gianotti et al. 2001). In contrast to the studies on delusion-prone participants, these subjects were not provided with any specific higher-order information.

We initially hypothesised in ***Study IV*** that delusion-prone subjects would show less fear learning in the non-instructed condition, than the control subjects - mirroring previous studies on classical conditioning and psychosis-related states (Balog et al. 2013; Holt et al. 2012; Holt et al. 2009; Jensen et al. 2008; Romaniuk et al. 2010). However, we did not observe any difference between the groups in this condition, and we did not observe any significant difference between the instructed and non-instructed condition in the delusion-prone group. The bias towards actively seeking meaning in incoming signals,

discussed in the previous paragraph, might underlie the absence of difference between instructed and non-instructed CS in delusion-prone individuals. Both instructed and non-instructed CS were presented at the same time. Thus, the instructions for the instructed CS might have prompted psychosis-prone individuals to look for special meaning in the non-instructed CS too, rendering them more similar to instructed CS in terms of contingency expectation. The combination of seeking for a meaning (as suggested by the initial given instructions for instructed CS) and the association with a aversive stimulation might have induced a more substantial learning than in a classical fear conditioning study where no information about possible contingencies is given at the start.

The need to look for meaning in all sorts of perceived objects might also relate to the fact psychosis-like experiences cannot be understood based on rational and commonly accepted explanations provided by the individual's culture. This is probably one of the reasons why those individuals tend to be interested in paranormal beliefs. By definition, the existence of paranormal phenomena is viewed by society as beyond normal experience or scientific explanation. Paranormal beliefs provide explanations to phenomena society fails to justify, similar to the way schizophrenia patients might feel about their experiences. While psychosis patients' own society marginalises them, and somewhat discredits the authenticity of their weird experiences by telling them these are "tricks of their brain", paranormal ideology is inclusive – it does not view psychotic individuals as ill – and gives credit to these unsettling perceptions by describing them as real. Paranormal beliefs, with their alternative and unconventional description of the world, provide individuals in psychosis-related states with readily available explanations that fit their strange experiences (something their own culture failed to achieve). Thus, psychotic or psychosis-prone individuals may be actively seeking information on paranormal topics as a more effective and less demanding way to attenuate the general confusion their unusual experiences generate. This is in line with both the idea we developed in ***Study IV*** and Kapur's description of delusion formation as an adaptive mechanism to aberrant salience (Kapur 2003).

In line with this idea, ***Study IV*** not only confirmed the larger influence of high-order instructions on delusion-prone individuals, but it also showed that those individuals integrated more readily externally generated complex (i.e. social) information that

would influence their belief system. Earlier work suggested that delusions were a response mechanism to aberrant salience attribution (Kapur 2003). Psychotic individuals would thus only fabricate those stories or beliefs after they had experienced those strange sensory phenomena, as a way to resolve the associated PEs. While not negating this theory, we extend it by proposing that delusion-prone individuals actively look for elements allowing them to generate those overly strong higher-order beliefs even in the absence of a specific aberrant sensory phenomenon. As mentioned previously, the vast majority of daily sensory processing happens at an automatic, non-conscious level. This is the case with background noise for instance. Conscious PE resolution usually occurs as a last resort, when the cognitive dissonance is too large to be resolved at a lower level. While non-conscious PE minimising can be seen as the default system in control individuals, we argue that due to the lack of reliable low-level prediction system, individuals are in a state of constant diffuse cognitive dissonance, leading them to use high-order level processing as their primary processing strategy. It is important to keep in mind that characteristic perceptual aberrations like hallucinations are not the only unsettling experiences that psychotic patients or psychosis-prone have. They also go through a whole range of more abstract sensations or feelings they can hardly verbalise. In the prodromal phase, they often describe being beset by feelings of a profound change, by the sense that something important is about to occur, without actually being able to pinpoint what exactly (Parnas & Handest 2003). Patients may experience some sort of "inner void" or "lack of inner nucleus" (Parnas & Handest 2003), or reflect on self-evident daily matters and get stuck on rumination loops due to failure to let things pass by (Parnas & Handest 2003). Those experiences can hardly be linked to one specific event. They rather correspond to a general sense of perplexity, related to hyper-reflexivity (Pérez-Álvarez et al. 2016; Sass & Parnas 2003). When viewing psychosis or psychosis-proneness in such a light, it then makes sense to postulate the existence of a bias towards a constant and proactive search and integration of higher order information/belief, in psychosis-related states, rather than viewing delusions as a mere consequence of aberrantly salient input (Kapur 2003).

d. Limitations

A main limitation that was present in all our studies (except ***Study II***) was the small size of our samples and the fact we only reached moderately high average PDI scores in our

delusion-prone groups. Ideally, in order to have a more complete understanding of psychosis, it would be best to study the whole spectrum or stratify the spectrum into several sub-groups. This would help get a clearer picture of the different aspects of delusion-proneness. The average PDI yes/no score on a population bases is approximately 6.7 (out of 21) (Peters et al. 2004). A score of 8 or 9 is commonly accepted as a reliable cut-off criterion differentiating high delusion-proneness from low delusion-proneness (Green et al. 2001; Preti et al. 2007; So & Kwok 2015). However, it is fair to assume someone scoring 9 on PDI is probably very different in terms of delusion-proneness than someone scoring 16. Nevertheless, so far in all studies working with psychosis tendencies, these two participants would be pooled in the same group and considered equal. Ideally, having a dimensional approach and study the whole spectrum without categorising participants would give a more accurate perspective. This is the approach we used in ***Study I***, but due to the skewed distribution of PDI in the general population, participants with high scores were largely under-represented compared to low scores. Such a situation thus makes it difficult to identify behaviours or response patterns that are characteristic of psychosis or psychosis-related states. An alternative option would be to include a control group and a delusion-prone group - with the latter being better defined. Nevertheless, the issue with finding enough participants would be the same, as exemplified in ***Study IV***, in which we had to screen 925 persons in order to include a total of 22 healthy male individuals in the final sample (scoring above 11 on PDI, and devoid of ADHD- or ASD-tendencies). Another idea would be to improve the characterisation of psychosis-prone individuals by adding other delusion-related questionnaires, and combining them with some psychosis biomarkers (including polygenic risk scores for schizophrenia). Another problem with self-report questionnaires like PDI is that they are subjective and susceptible to interpretation biases, lack of cognitive insight, etc. Thus, the use of biomarkers represents a useful addition to psychosis-proneness definition as they allow assessing some other psychosis-related features in a more objective way. Finally, the present studies have to be performed in psychosis patients as well to understand whether the findings generalize to clinical phenotypes, as has been done previously (Teufel et al. 2015).

A limitation related to ***Study III*** was the fact that unlike the original study where participants were asked to elaborate on the reasons behind their choice, here

confabulation was only measured indirectly by the negative preference ratings. This verbal reporting was removed due to technical limitations in our setting. However bringing back this part of the original paradigm (either through verbal or written report) would provide a more detailed account of confabulations.

As for ***Study IV***, the main limitation was the fact the non-instructed condition failed to be a fully reliable control condition. Compared to classical conditioning paradigms in which participants are not being given any explicit instructions about the pairing of unconditioned and conditioned stimuli, in our paradigm, the non-instructed faces were presented at the same time as the instructed stimuli. Thus, the effect of instructions (in particular the negative one) on participants' judgments was translated on the non-instructed faces as well. During the debriefing session following the experiment, a large number of participants actually reported that after the instruction phase, they expected at least of one the two non-instructed faces to give them shocks. This suggests that unlike our initial thought when constructing the paradigm, the non-instructed faces were not purely non-instructed. This was also in line with the absence of a significant fear index score difference between those two conditions after the acquisition phase. Surprisingly, while participants indicated that that had built some priors about the non-instructed faces following the instruction phase, this did not actually translate into their ratings, as there was no difference in the non-instructed fear index scores before and after the instruction phase. One could speculate that the prior that was built regarding the non-instructed faces was low in precision as it solely indicated that one face would most likely give shocks, however both faces were equally susceptible to be the shock one. Therefore, although there was an existing prior, it was too imprecise to bias the ratings. However, the expectation stating that one of the non-instructed faces was going to give them shocks combined with the presence of shocks during the acquisition phase (confirmatory evidence), probably led to a stronger reappraisal of the non-instructed faces in psychosis-prone individuals.

e. Future directions

The four studies presented in this thesis confirmed the usefulness of studying psychosis-proneness when trying to understand mechanisms behind psychosis. Despite being healthy and thus not subjected to medication effects, delusion-prone

individuals show behavioural and cognitive resemblances to patients. As suggested in our different studies, psychosis-prone individuals differ significantly from controls in a variety of behavioural responses and brain activity patterns. The work gathered here, therefore argues for more studies taking into account psychosis-proneness and not only focusing on clinical states. Studies using both patients and delusion-prone groups would greatly help the field move forward. ***Study II*** also brings further evidence regarding the existence of overlaps between psychosis-proneness and other neurodevelopmental disorders like ADHD. This stresses the importance of assessing these tendencies when studying psychosis-related states in order to avoid describing behaviours that actually pertain to ADHD or ASD symptomatology as specifically psychosis-related.

1. Choice blindness

A challenging aspect in the paradigm used in ***Study III*** is the fact that, although it is fairly reasonable to consider the task taps onto the low end of the processing hierarchy, it is not clear to what extent the instruction/training session (only containing non-manipulated trials) represent an instruction phase, leading participants to create an explicit belief (high-level prior) about the paradigm; i.e. the picture that reappears is (unquestionably) the one on which she/he clicked. Consequently, it is hard to draw a clear conclusion on the results, since part of the observations might be due to a larger top-down effect of this high-order belief in delusion-prone individuals. The belief that they have full control over the task, thus meaning the picture they see has to be the one they selected, would thus overwrite the incoming stimulus. Removing the training session could help limit the probability of unwanted induction of beliefs and would allow focusing on low-level processes. Considering the task is quite self-explanatory, removing the training part would not affect the understanding the rules of the paradigm.

An interesting way to move forward with the choice blindness paradigm would be to look separately at the two levels and show a double dissociation in terms of behaviours, depending on which level is targeted (similar to ***Study IV***). This could be achieved by having the first two groups (delusion–prone group 1 and control group 1) go through the same paradigm as in ***Study III*** (without training). There, the focus would be on low-

level processes. The two other groups (delusion-prone group 2 and control group 2), participants would be explicitly informed that in this part, a significant number of trials would be manipulated, while in practise none would be. There, the effect of high-level beliefs on lower level processes would be investigated. In line with our results in ***Study III***, we would expect delusion-prone participants to detect fewer manipulations than controls in the first part. However, the larger effect of high-level top-down regulation associated with psychosis-proneness would lead delusion-prone participants to be more inclined than controls to report false detections in the second part.

In addition, as discussed previously, it would be of great interest to investigate whether confabulations related to the non-detected manipulated trials differ in frequency, length and vividness between delusion-prone subjects and controls. This can be done using an automatic linguistic analysis of the verbal responses given by the subjects. Finally, formal models of decision-making could be applied to the paradigm.

2. Instructed learning

An appealing aspect of the instructed learning paradigm is the fact it induces delusion-like beliefs pertaining to social interactions, which thus mimic some aspects of paranoid delusions, like persecutory ideation. Paranoid beliefs are some of the most common symptoms in schizophrenia (Freeman 2007; Insel 2010). They are the consequence of dysfunctional advanced reasoning processes such as causal inference or mentalising, resulting in misjudgement of other people's intentions towards oneself. Studying the formation of paranoid beliefs may help understand which high-level mechanisms are compromised in psychosis.

Similar to other kinds of delusion, persecutory ideation is often associated with belief inflexibility. ***Study IV*** pointed slightly towards this idea when reporting delusion-prone individuals not only showed resistance to extinction but they actually tended to display reinforced judgement following this phase. This aspect could be further investigated with this paradigm, in order to mirror results in studies showing BADE and jumping-to-conclusion bias in schizophrenia (Buchy et al. 2007; Woodward et al. 2006; Eisenacher & Zink 2016), but using a more ecological model. In ***Study IV***, these two kinds of information about UCS contingencies (bottom-up sensory input and top-down

high-order belief) were congruent. If one assumes that the weight of high-level priors is much larger than the weight of low-level expectations in delusion-prone individuals, then high-level top-down signals may overwrite weak incoming sensory input when facing contradictory information, mirroring the BADE phenomenon (Buchy et al. 2007; Eisenacher & Zink 2016; Veckenstedt et al. 2011). This hypothesis could be tested with the instructed learning paradigm, by inverting the contingencies of the instructed CS. Namely, the instructed CS- (presented as a virtuous person) would actually turn out to be the one associated with shocks, while the instructed CS+ (presented as a threatening person) would not be paired with shocks. This version of the paradigm would be somewhat similar to a recent study, where the delusion-proneness was not investigated (Atlas et al. 2016). Introducing an online monitoring of the likability for the 4 CS would allow to follow and model the dynamic changes in participants' judgment. According to our hypothesis we would expect delusion-prone individuals to stick longer to their initial judgement (i.e. more negative ratings to the initial instructed CS+ and more positive ratings to the initial instructed CS-), while controls would reverse their judgement more rapidly.

The instructed learning paradigm explored the high-versus-low dissociation in the context of negative emotions. However it would also be interesting to study this imbalance between high and low-levels in positive emotions and reward framework too, especially considering the central role dopamine plays in reward processing (Schultz 2016). Nevertheless, reward processing and experience depend largely on the value people attribute to stimuli and can thus vary greatly across individuals, which may make it difficult to successfully implement a paradigm on reward in an experimental setting. This might partly explain contradicting results suggesting for instance impaired positive emotion processing in schizophrenia (Herbener et al. 2007) whereas others only noted biases towards negative emotional stimuli (Kohler et al. 2003), or some reporting reduced experience of reward and motivation (Fervaha et al. 2017; Fervaha et al. 2015). These contradictory observations speak towards the need of studies using more ecological reward paradigms, in which different processing levels could be targeted, similar to our instructed learning experiment.

Another aspect that deserves a greater attention and the notion of confidence displayed by individuals in psychosis-related states. Previous work has shown patients with

schizophrenia were not only more prone to making wrong decision or perceptual mistakes, but they were also often more confident in their performance than control participants (Joyce et al. 2013; Moritz et al. 2005; Moritz et al. 2014; Jardri & Denève 2013; Buchy et al. 2009). It is commonly suggested that such an overconfidence bias probably plays a role in the maintenance of delusions even in the face of contradicting information. In ***Study III*** we only touched upon this aspect, using preference ratings as a proxy to uncertainty, but future studies should integrate this dimension more precisely. Adding metacognitive tasks (Fleming & Lau 2014; Fleming et al. 2012) in order to evaluate participants' cognitive insight would be a useful complement to psychosis-proneness assessment.

Finally, another interesting aspect to consider for future studies, and in particular the instructed learning and choice blindness paradigms, would be to adopt a more computational perspective on the behavioural and functional imaging analyses. Computational models have been used to better describe reward learning (Pessiglione et al. 2006) as well as instructed fear learning paradigms (Atlas et al. 2016). Especially, it would be interesting to study multi-level predictive coding using models such as hierarchical Gaussian filter (Powers et al. 2017). Such models have recently been implemented in experimental studies of psychosis (Powers et al. 2017; Schmack et al. 2016). This would help capture more complex aspects of the different mechanisms involved in the psychosis-related behaviours we aim to understand.

3. Pharmacological manipulations

Another interesting future direction would be to combine the paradigms we have designed with pharmacological manipulations. The role of dopamine in salience attribution makes the use of dopamine agonists very interesting in that context. In line with the dopamine hypothesis of schizophrenia (Howes & Kapur 2009), one could test whether the use of dopamine agonists could reproduce in non-delusion-prone individuals, the findings observed in delusion-prone participants. For instance one could hypothesise a dopamine agonist would lead to a decreased manipulation detection rate in the choice blindness paradigm or a larger effect of instructions.

The NMDA-R system also appears as another interesting target. Due to the slow

dynamics of NMDA-R it is proposed that these receptors are mainly involved in representing high-level top-down predictions, while the rapid AMPA-R neurotransmission seem more appropriate to the specification of prediction errors (bottom-up processes) (Corlett et al. 2011; Friston 2005). Together with the involvement of NMDA-R in the generation of transient memory traces used to predict incoming stimuli (Javitt et al. 1998; Javitt et al. 1993; Atkinson et al. 2012; Brockhaus-Dumke et al. 2005) it seems NMDA-R are involved in top-down signalling in all levels of the processing hierarchy. It would therefore be interesting to test whether ketamine administration in healthy low-delusion-prone individuals would also lead to decreased detection rate in choice blindness or an increased influence of instructions on fear learning, mimicking the results we reported in delusion-proneness in ***Study III*** and ***Study IV***.

f. Conclusion

We believe the four studies presented here contribute to the advancement of the field by bringing novel supporting evidence to the hypothesis of a co-existence of impaired unstable low-level processing systems and overly strong high-level expectations in psychosis-related state. Using paradigms that allowed us to investigate different cognitive domains (self-recognition, decision making, fear learning and social judgment), we reliably demonstrated that when facing perceptual ambiguity, delusion-prone individuals compensated their lack of a reliable low-level expectation system either with aberrantly salient bottom-up sensory input (***Study I*** and ***III***), or by relying on overly strong beliefs, once those were successfully induced (***Study IV***).

More importantly, we further this idea by showing that the increased top-down influence of those higher-order beliefs was not simply a secondary mechanism. Instead, we argue it actually represents a proactive strategy for individuals in psychosis-related states, to make sense of the noisy environment in which they are living. These individuals are constantly seeking new high-order beliefs to integrate in their models of the world in order to reduce this persistent feeling of cognitive dissonance.

In addition to offering interesting results, the four studies presented here should be viewed as a starting point, opening to more studies. More than testing and bringing

support to our hypotheses, our work raised new questions that require further investigations, building on our results and the optimisation of our paradigms.

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Appendix

Peters' Delusion Inventory – 21-item version. Reprinted from Peters E., Joseph S., Day S., Garety P., *Measuring Delusional Ideation: The 21-Item Peters et al. Delusions Inventory (PDI)*, Schizophrenia Bulletin, 2004, 30, 4, 1005-1022, by permission of Oxford University Press.

Appendix

P.D.I.-21

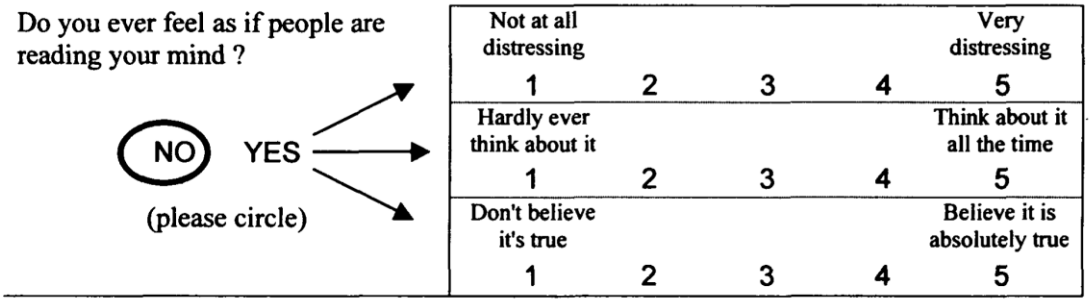
This questionnaire is designed to measure beliefs and vivid mental experiences. We believe that they are much more common than has previously been supposed, and that most people have had some such experiences during their lives. Please answer the following questions as honestly as you can. There are no right or wrong answers, and there are no trick questions.

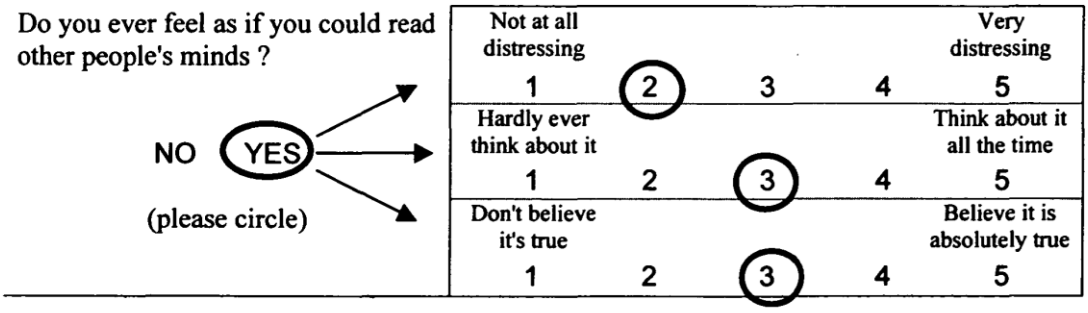
Please note that we are NOT interested in experiences people may have had when under the influence of drugs.

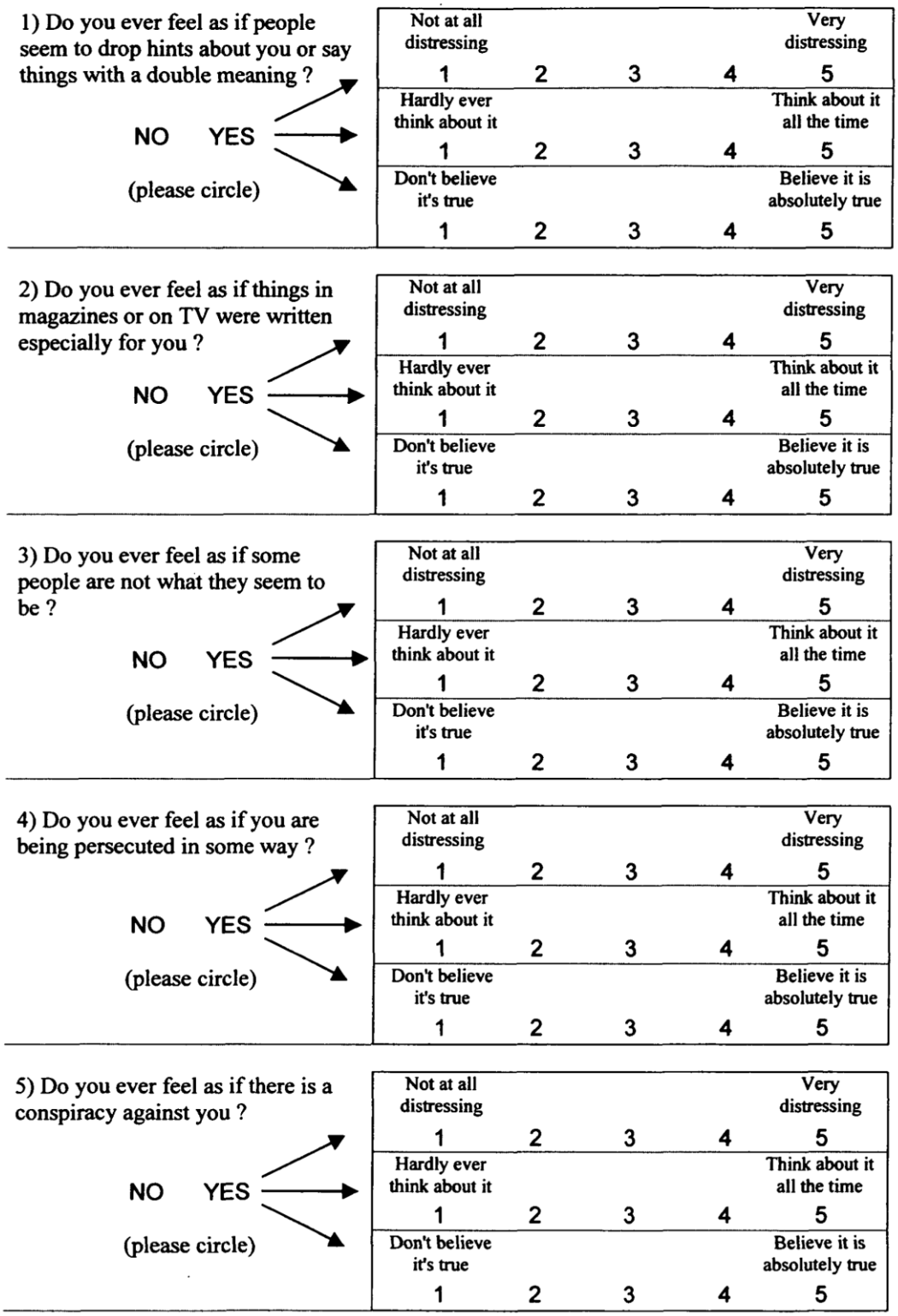
IT IS IMPORTANT THAT YOU ANSWER *ALL* QUESTIONS.

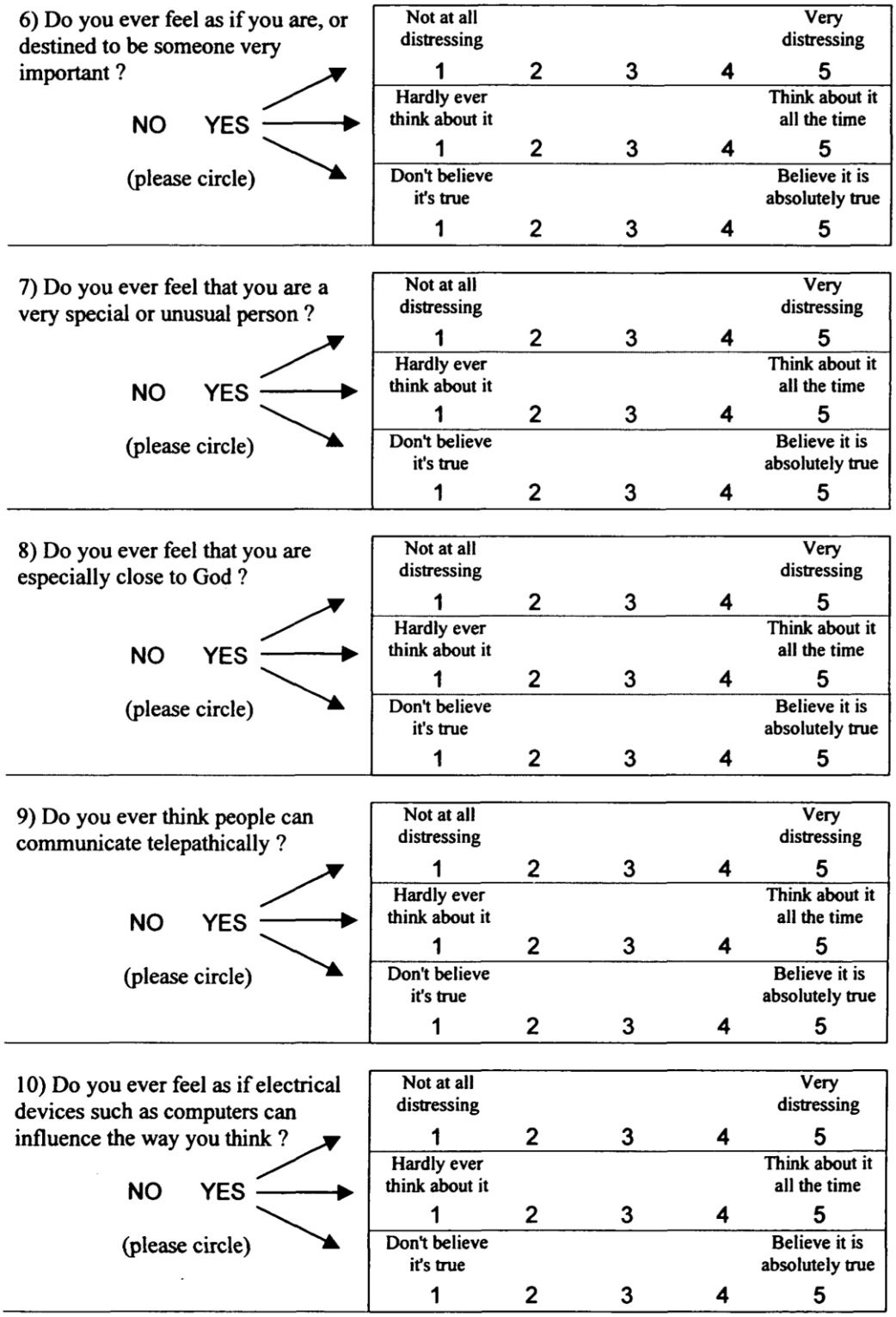
For the questions you answer YES to, we are interested in:
(a) how distressing these beliefs or experiences are
(b) how often you think about them; and
(c) how true you believe them to be.
On the right hand side of the page we would like you to circle the number which corresponds most closely to how distressing this belief is, how often you think about it, and how much you believe that it is true.
If you answer NO please move on to the next question.

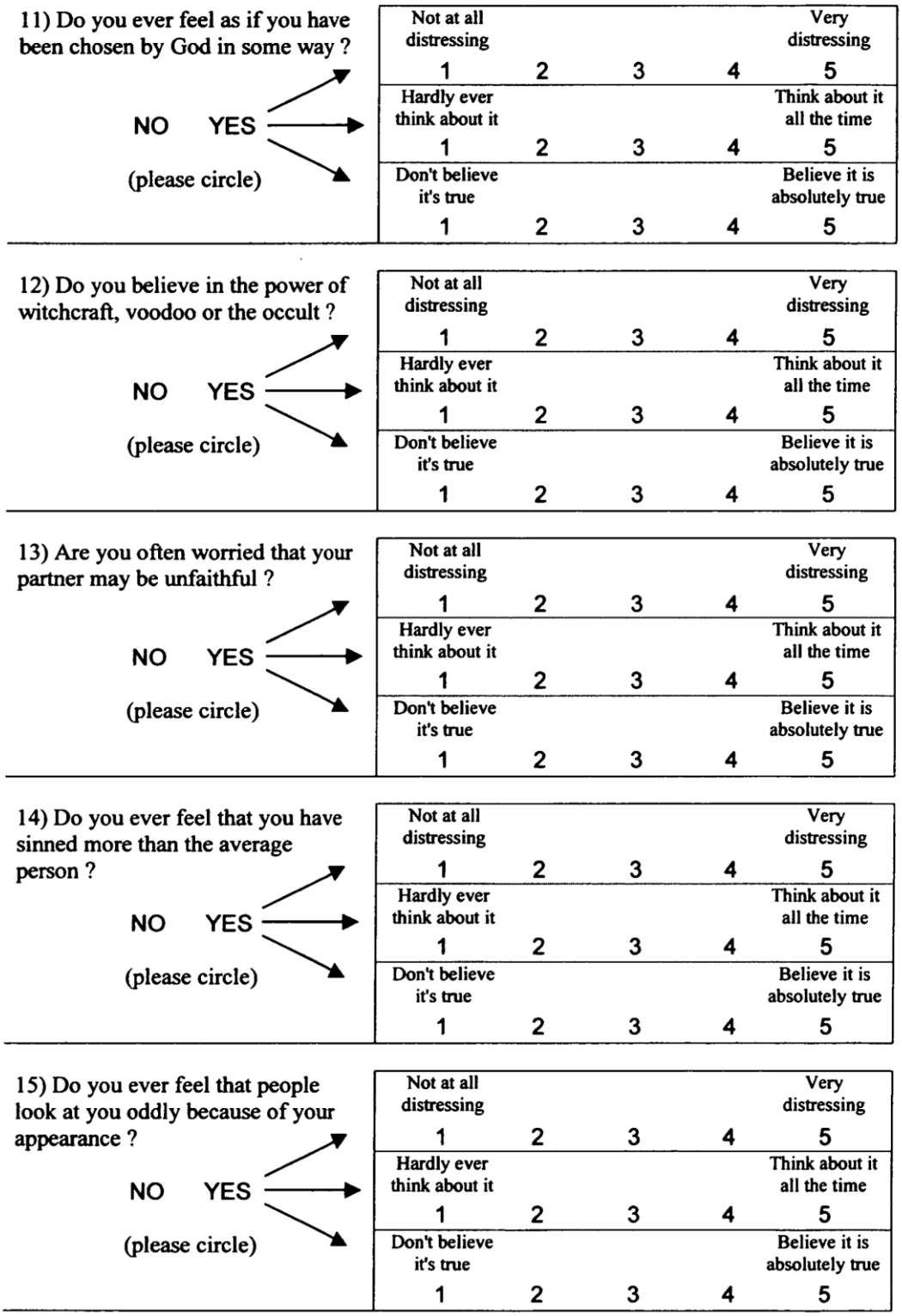
Example






1) Do you ever feel as if people seem to drop hints about you or say things with a double meaning ?
NO YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5
2) Do you ever feel as if things in magazines or on TV were written especially for you ?
NO YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5
3) Do you ever feel as if some people are not what they seem to be ?
NO YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5
4) Do you ever feel as if you are being persecuted in some way ?
NO YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5
5) Do you ever feel as if there is a conspiracy against you ?
NO YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5


6) Do you ever feel as if you are, or destined to be someone very important ?
NO YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5
7) Do you ever feel that you are a very special or unusual person ?
NO YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5
8) Do you ever feel that you are especially close to God ?
NO YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5
9) Do you ever think people can communicate telepathically ?
NO YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5
10) Do you ever feel as if electrical devices such as computers can influence the way you think ?
NO YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5


11) Do you ever feel as if you have been chosen by God in some way ?
NO YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5
12) Do you believe in the power of witchcraft, voodoo or the occult ?
NO YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5
13) Are you often worried that your partner may be unfaithful ?
NO YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5
14) Do you ever feel that you have sinned more than the average person ?
NO YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5
15) Do you ever feel that people look at you oddly because of your appearance ?
NO YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5

16) Do you ever feel as if you had no thoughts in your head at all ?

NO YES

(please circle)

Not at all distressing				Very distressing
1	2	3	4	5
Hardly ever think about it				Think about it all the time
1	2	3	4	5
Don't believe it's true				Believe it is absolutely true
1	2	3	4	5

17) Do you ever feel as if the world is about to end ?

NO YES

(please circle)

Not at all distressing				Very distressing
1	2	3	4	5
Hardly ever think about it				Think about it all the time
1	2	3	4	5
Don't believe it's true				Believe it is absolutely true
1	2	3	4	5

18) Do your thoughts ever feel alien to you in some way ?

NO YES

(please circle)

Not at all distressing				Very distressing
1	2	3	4	5
Hardly ever think about it				Think about it all the time
1	2	3	4	5
Don't believe it's true				Believe it is absolutely true
1	2	3	4	5

19) Have your thoughts ever been so vivid that you were worried other people would hear them ?

NO YES

(please circle)

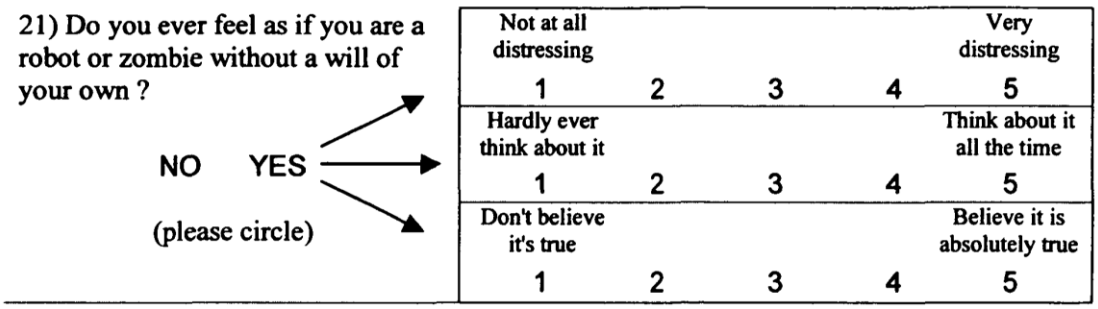
Not at all distressing				Very distressing
1	2	3	4	5
Hardly ever think about it				Think about it all the time
1	2	3	4	5
Don't believe it's true				Believe it is absolutely true
1	2	3	4	5

20) Do you ever feel as if your own thoughts were being echoed back to you ?

NO YES

(please circle)

Not at all distressing				Very distressing
1	2	3	4	5
Hardly ever think about it				Think about it all the time
1	2	3	4	5
Don't believe it's true				Believe it is absolutely true
1	2	3	4	5


21) Do you ever feel as if you are a robot or zombie without a will of your own ?
NO
YES
(please circle)
Not at all distressing
Very distressing
1 2 3 4 5
Hardly ever think about it
Think about it all the time
1 2 3 4 5
Don't believe it's true
Believe it is absolutely true
1 2 3 4 5

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