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The Effects of Positive and Negative Schizotypy on Prepulse Inhibition and Cognitive Functions

MSc Thesis

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Abstract

High schizotypal traits in the general population are conceptualized as part of a continuum in the liability to schizophrenia, which ranges from mild schizotypal traits, and schizotypal personality disorder to deteriorating schizophrenia. Previous studies have found a correlation between schizotypal traits and deficient cognitive functions as well as Prepulse Inhibition of the acoustic startle reflex (PPI), as in schizophrenia. However, significantly fewer studied have focused on the different dimensions, which constitute the construct of schizotypy and their subsequent effects on cognition and PPI. This thesis presents the concept of Cognitive-Perceptual (Positive symptomatology) and Interpersonal (negative symptomatology) schizotypal dimensions, as measured with the psychometric "Schizotypal Personality Questionnaire" (SPQ) instrument, and examines their effect on schizophrenia-related endophenotypes (cognitive functions and PPI) in healthy individuals in the general population.

Cognitive functions were assessed using a broad range of neuropsychological tasks and the startle response was recorded using an electromyographic startle system. First, a principal component analysis (PCA) was conducted to group all the cognitive variables into related factors. Then, regression analyses were run, in order to identify possible associations. Finally, we grouped our subjects into "Non-Schizotypal Prone, "High Positive Schizotypal" and "High Negative Schizotypal" groups, based on their scores in the Cognitive-Perceptual and Interpersonal indices of the SPQ.

Significant correlations were found between the Cognitive-Perceptual index and the cognitive factors "Perseveration", "Problem Solving", "Declarative Memory", and "Episodic Memory". Moreover, significant correlations were found between the Interpersonal index and "Inattention" and "Declarative Memory". No correlation was

found between the Cognitive-Perceptual or the Interpersonal dimension of schizotypy and PPI.

These findings suggest that although healthy individuals with positive or negative schizotypal traits share some cognitive deficits, PPI deficits may be more specific to schizophrenia and schizotypal personality disorder. The limitations of the study are also discussed.

Part A’
Introduction

Chapter 1
Introduction to the Schizophrenia Spectrum

Schizophrenia spectrum disorders comprise a group of psychiatric diagnoses that share several clinical features, typically involving reality distortion. Spectrum conveys the idea that the disorders are somehow similar to each other regarding either the clinical symptoms, or the disease mechanism and the etiology (Heckers, 2009).

Schizophrenia has a multifactorial etiology, significant heterogeneity of signs, symptoms, disease course and outcome, with multiple susceptibility genes interacting with environmental insults to yield a range of phenotypes in the spectrum.
Based on this, the classification of distinct disorders in the schizophrenia spectrum is well justified. First, these disorders could represent a mild form of schizophrenia. In addition, they may be genetically associated with severe schizophrenia but not resemble the clinical aspects of the disease. Second, the disorders of the spectrum may occur more often in families of schizophrenics than in control-comparison groups. Third, the disorders may resemble severe schizophrenia regarding the clinical aspect, but they are not genetically associated with it (Heckers, 2009).

The historical aspects of the classification of these disorders in a spectrum can be traced back in 1890. Emil Kraepelin established a categorical model of poor versus good outcomes of a disease and presented, for the first time, dementia praecox (emotional dullness, lack of interest and apathy) and manic-depressive disorder as two naturally-occurring disease entities (Blaney et al, 2009).

The concept of the Schizophrenia spectrum was also found in the work of Bleuler (1911) on Dementia Praecox or "the Group of Schizophrenias". Bleuler extended the definition of dementia praecox to include people with less severe dementia praecox symptoms and better prognosis. Specifically, he stated that schizophrenia "is not a disease in the strict sense, but appears to be a group of diseases." Moreover, he was the first to describe symptoms such as "positive" or "negative", and recognized that these symptoms tended to cluster into distinct categories.

However, the term "schizophrenia spectrum" was established in 1968 by Kety et al. who performed adoption studies in a Danish population. They discovered that some relatives of the schizophrenia patients, who did not have the disorder, exhibited symptoms similar to a borderline state of schizophrenia. In general, Kety et al. thought of schizophrenia, as a syndrome, or a collection of symptoms, which seem to hang together and lead to a variety of manifestations. Due to the study of Kety et al, disorders that are genetically related with schizophrenia were included in the spectrum.

As a conclusion, the concept of schizophrenia spectrum disorders is the result of a categorical diagnostic system and supports the idea that schizophrenia is the one extreme of a continuum, and is a phenotypic representation of a liability to functional psychoses.

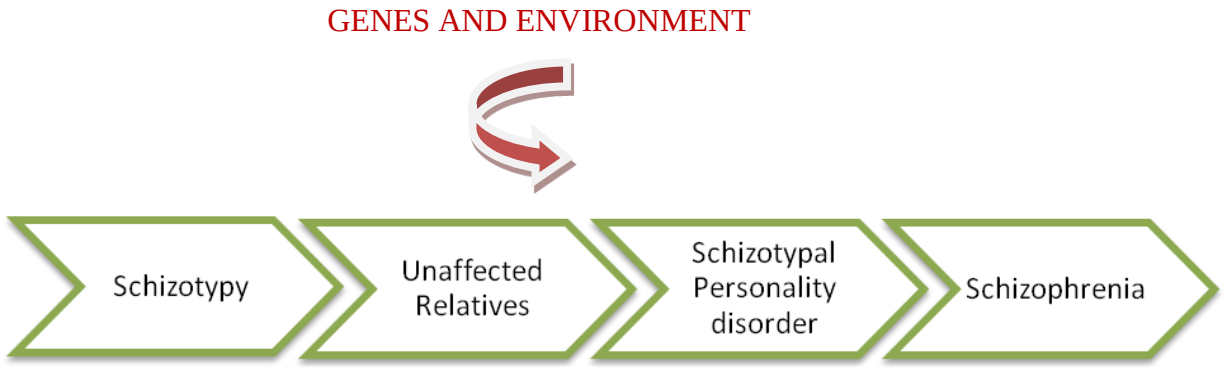

Figure 1.**The Schizophrenia Continuum**

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR, 1994), the schizophrenia spectrum consists of typical schizophrenia, two forms of schizophrenia with shorter duration (i.e., schizophreniform disorder and brief psychotic disorder), two delusional disorders (i.e., delusional disorder and shared psychotic disorder), and three personality disorders with features that resemble schizophrenia (i.e. schizotypal, paranoid, and schizoid personality disorder). In addition, the diagnosis of schizoaffective disorder in the spectrum captures psychotic patients with significant mood symptoms.

Schizophrenia is a disorder that lasts for at least six months and includes at least a month of active-phase symptoms (two [or more] of the following: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms). It is characterized by social, cognitive and occupational dysfunction. Schizophrenia is discriminated in 5 subtypes, catatonic, disorganized, paranoid-hallucinatory, undifferentiated and residual. Each one of these subtypes has different core symptoms. Its prevalence is 1% in the general population and the disease onset is between the age of 18 to25 for men and 25 to 30 years for women.

Schizophreniform Disorder is characterized by a symptomatic presentation that is equivalent to Schizophrenia except for its duration (i.e., the disturbance lasts from at least 1 month but less than 6 months) and the absence of a requirement of a decline in functioning. The incidence is low, possibly fivefold less than that of Schizophrenia. One third of patients with initial diagnosis of schizophreniform disorder recover within 6 months, the remaining two thirds will progress to diagnosis of Schizophrenia.

Brief Psychotic Disorder is defined by the presence of delusions, hallucinations, disorganized speech, or grossly disorganized or catatonic behavior lasting for at least 1 day but for less than 1 month and the individual eventually has a full return to the premorbid level of functioning.

Delusional Disorder is defined by the presence of one or more non bizarre delusions that persist for at least 1 month. Apart from the direct impact of the delusions,

psychosocial functioning is not markedly impaired, and behavior is neither obviously odd nor bizarre. The type of the disorder can be specified according to the delusion theme as, erotomanic type, grandiose, jealous, persecutory, somatic, mixed and unspecified type. Individuals with delusional disorder do not appear to have an increased familial risk of schizophrenia spectrum disorders or vice versa.

Shared Psychotic Disorder is characterized by a delusion that develops in an individual who is involved in a close relationship with another person, who already has a Psychotic Disorder with prominent delusions. The individual comes to share the delusional beliefs of the primary case in whole or in part. Impairment is often less severe in the individual with Shared Psychotic Disorder than in the primary case. If the relationship with the primary case is interrupted, the delusional beliefs of the other individual usually diminished or disappear.

Schizotypal Personality disorder begins early in adulthood and is defined by a pattern of acute discomfort in close relationships, cognitive or perceptual distortions, and eccentricities of behavior. An individual diagnosed with Schizotypal personality disorder suffers from at least 5 of the following symptoms, ideas of reference, odd beliefs or magical thinking, unusual perceptual experiences, suspiciousness, odd speech, constricted affect, lack of close friends, eccentric behavior, and excessive social anxiety. Schizotypal Personality Disorder has been reported to occur in approximately 3% of the general population.

Schizoid Personality disorder is a pattern of detachment from social relationships and a restricted range of emotional expression that occurs early in adulthood. The disorder appears to be intermediate between schizotypal and paranoid personality disorders with regards to its genetic relationship to schizophrenia. An individual with Schizoid personality disorder express symptoms such as flattened affectivity, no interest of having sexual experiences with another person, neither desires nor enjoys close relationships, lacks of close friends, that individual chooses solitary activities, and takes pleasure in a few activities.

Paranoid Personality disorder is a pattern of distrust and suspiciousness such that others' motives are interpreted as malevolent. For a diagnosis there must be four or

more of the following symptoms: suspiciousness that others are exploiting/harming/deceiving, preoccupation with doubts about others' trustworthiness, reluctance to confide in others, reading hidden meaning into benign remarks/events, persistent grudges, perceiving attacks on character or reputation, and recurrent suspicions regarding fidelity of partner.

Schizoaffective Disorder lives in the borderland between schizophrenia and mood disorder. It is a disorder in which a mood episode and the active phase symptoms of Schizophrenia occur together and were preceded or are followed by at least 2 weeks of delusions or hallucinations without prominent mood symptoms.
Schizoaffective Disorder appears to be less common than Schizophrenia. Typical age at onset of Schizoaffective Disorder is early adulthood the prognosis for Schizoaffective Disorder is somewhat better than the prognosis for Schizophrenia, but considerably worse than the prognosis for Mood Disorders

Table 1.The Schizophrenia Spectrum

SPECTRUM DISORDER	TYPE OF DISORDER	DURATION	ONSET	SYMPTOMS	PREVALENCE
SCHIZOAFFECTIVE DISORDER	Psychotic and Mood disorder	At least 2 weeks of delusions or hallucinations in the absence of mood symptoms	Early adulthood	Delusions, hallucinations depression or mania	0.5% -0.8%
PARANOID PERSONALITY DISORDER	Personality disorder	Lifelong condition	Early adulthood	distrust and suspiciousness	0.5%-2.5% in the general population
SCHIZOID PERSONALITY DISORDER	Personality disorder	Lifelong condition	Early adulthood	detachment from social relationships restricted range of emotional expression	Uncommon in clinical settings

SCHIZOTYPAL PERSONALITY DISORDER	Personality disorder	Lifelong condition	Early adulthood	acute discomfort in close relationships, cognitive or perceptual distortions, eccentricities of behavior	3% in the general population
SHARED PSYCHOTIC DISORDER	Delusional disorder	Chronic without intervention		delusion in an individual who is influenced by someone who has a longer-standing delusion with similar content.	Is not known
BRIEF PSYCHOTIC DISORDER	Psychotic disorder	More than 1 day less than 1 month	late 20s or early 30s	delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior	Is not known
SCHIZOPHRENIFORM DISORDER	Psychotic disorder	From 1 to 6 months	18-24 years in men 24-35 years in women.	symptomatic presentation equivalent to Schizophrenia	Low incidence possibly 5fold less than that of Schizophrenia
SCHIZOPHRENIA	Psychotic disorder	At least 6 months	18 to25 years for men 25 to30 years for women	delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative	1% in the general population

				symptoms	
DELUSIONAL DISORDER	Delusional disorder	At least 1 month	from adolescence to late in life.	Non bizarre delusions	0,7 % in the general population

Chapter 2
Definition of Schizotypy & Historical aspects

Schizotypy is a heterogeneous construct and is used in two different ways in the scientific practice. On the one hand, there is the psychiatric viewpoint, which emphasizes the psychosis-proneness of schizotypy and accepts the fact that schizotypy is a part of the schizophrenia spectrum. On the other hand, there is the psychological viewpoint, which emphasizes the personality aberrations of schizotypy and classifies it, as a personality disorder (Tarbox et al, 2011)

According to the psychiatric viewpoint, schizotypy is defined as an inherited vulnerability state genetically related to schizophrenia. Schizotypy represents attenuated psychotic symptoms and is a forerunner of schizophrenia (Meehl, 1990). The groundwork of Meehl's theory can be found in the clinical observations of S. Rado, (1953). Historically, Rado, while attempting to link genetic influences for schizophrenia, coined the term schizotypy, in order to represent a condensation of the schizophrenic phenotype (Lenzenweger, 2010). Schizotypal disorders refer to people genetically predisposed to schizophrenia who will not proceed to the development of the full symptomatology. An individual possessing the schizophrenic phenotype was a schizotype, whereas the correlated traits deriving from this "type" were termed "schizotypal organization" and the overt behavioral manifestations of the schizotypal traits were termed "schizotypal behavior". Moreover, Rado suggested that a schizophrenia diathesis lies on a continuum that could lead to a variety of phenotypes (Rado, 1960).

All these viewpoints were taken into account by Meehl, who suggested a model of the pathogenesis of schizophrenia and introduced the terms schizotaxia and schizotypy. Schizotaxia is a neurophysiological defect, essential for the development of schizophrenia but not "enough". In a healthy environment, individuals with genetic schizotaxial vulnerability are prone to develop schizotypal traits. Nevertheless, only a small group of these people will display schizophrenia depending on environmental circumstances such as negative life experiences (Meehl, 1989).
Meehl's model incorporates the fact that, although most individuals expressing schizotypal traits will never develop a clinical form of psychosis they will exhibit a series of cognitive, behavioral, social, psychophysiological and neurobiochemical alterations that establish their risk status (Raine, 2006).
Therefore, Meehl's etiologic model of schizophrenia assumes that both schizotypal and schizophrenic individuals share a common neurodevelopmental vulnerability path. Schizotaxic individuals, who have a genetic vulnerability, will display schizotypy on a continuum of increasing severity, depending on the influence of negative life experiences and other personality traits (Raballo et al, 2011).

Unlike the views of Rado and Meehl, Claridge worked on the psychological aspect of schizotypy and described the term as a trait, characterized by certain cognitive features and psychotic-like phenomena, which are part of the general system of personality. Claridge's theory supports the idea that schizotypy is an aberrant/deviant personality trait, non-pathological, similar to Schizotypal Personality Disorder (SPD). The main difference between these two, lays on the fact that schizotypy is less severe than SPD, with lower levels of distress and unaffected social and occupational functioning (Claridge, 1997).

Schizotypal personality traits are normally distributed in the general population (Raine, 1991), and are more often found among the biological relatives of schizophrenic individuals (Kotsaftis et al, 1993). A continuum of severity is suggested, ranging from mild schizotypal traits, moderate schizotypal personality disorder or SPD (DSM-IV), to deteriorating schizophrenia (Wolff et al, 1991).

Schizotypal traits in the general population are frequently co-expressed with other personality traits such as the self transcendence, harm avoidance, anxiety and

depression, similarly to schizophrenia patients. Specifically, schizophrenia patients have been found to score higher in Harm Avoidance (Guillem et al, 2002; Kurs et al, 2005) and lower in Reward Dependence (Kurs et al, 2005; Ritsner et al, 2004), Self Directedness and Cooperativeness (Guillem et al, 2002) compared with healthy individuals. Cloninger et al, (1993) proposed that a specific configuration of character (i.e. high Self Transcendence, low Cooperativeness and Self Directedness) may be indicator of proneness to psychosis. First degree relatives of schizophrenia patients also score higher in Harm Avoidance and Self Transcendence (Bora et al, 2007; Smith et al, 2008) in comparison with control subjects. In non clinical samples with high schizotypal traits, high Self-Transcendence and Harm Avoidance and low Self-Directedness, seem to confer a greater risk for schizotypy (Daneluzzo et al, 2005; Hori et al, 2012). As a matter of fact, in the studies of Daneluzzo et al, (2005) and Bora et al, (2007), the interpersonal factor (i.e. negative schizotypy) of the SPQ was correlated positively with harm avoidance and the cognitive–perceptual factor (i.e. positive schizotypy) was correlated positively with self-transcendence.

Mood and anxiety symptoms are also present in patients with schizophrenia (Elk et al, 1986). Anxiety and depression appear to be strongly associated with the positive factor of schizophrenia (Emsley et al., 1999). DSM-IV-TR indicates that over half of all patients with schizotypal personality disorder experience at least one episode of major depression and first degree relatives of schizophrenia patients experience elevated rates of major depressive disorder (Baron et al, 1991). Furthermore, anxiety and depression have been found to correlate with positive schizotypal symptoms using the O-LIFE and the Schizotypal Personality Scales (Day et al, 1999). Positive schizotypy is more closely associated with anxiety and depression than the interpersonal dimension of schizotypy in non-psychotic psychiatric patients (Lezenweger et al, 1989) and healthy individuals from the general population (Lewandowski et al, 2006).

Taking into consideration all the aforementioned aspects of schizotypy, it is important to examine schizotypal traits, as they are thought to reflect liability for schizophrenia (Meehl, 1962) and schizotypy research might provide evidence about the nature of liability for schizophrenia (Lenzenweger,1999). Furthermore, understanding the nature of schizotypal traits could provide an explanation for the development of

schizophrenic symptoms. A main advantage of schizotypal research is that it does not involve some confounds present in research on people with schizophrenia e.g., effects of antipsychotic medication (Oltmanns et al, 1980) and as a result it can provide important evidence to research on schizophrenia.

Chapter 3
Etiology of Schizotypy & Symptom Classification

Although, the etiology of schizotypy is not fully understood, it is suggested that the construct shares a similar etiology to schizophrenia (Barkus et al, 2006). Individuals having schizotypal traits show similar deficits in brain structure and function as individuals diagnosed with psychosis (Byrne et al, 1999). For example, individuals with high schizotypy scores also have increased levels of dopamine (Mohr et al, 2004) and the Catechol-O-methyltransferase Val158Met genotype may affect the expression of schizotypy by direct or indirect effects on central dopamine neurotransmitter signaling (Stefanis et al, 2004). Other studies have shown that gray matter volume in the prefrontal cortex of schizotypal individuals is reduced (Diwadkar et al, 2006) and an association between neuregulin-1 (which is associated with schizophrenia by Harrison et al, 2005), and perceptual aberration in adolescents (Lin et al, 2005) has been reported. Also, early life characteristics, such as lower placental weight, lower birth weight, smaller head circumference at 12 months and environmental factors (e.g. lower family socioeconomic status, winter/autumn birth and maternal smoking during pregnancy) may play a special role in predicting schizotypal traits in adulthood (Lahti et al, 2009) as has been found in schizophrenia (Hultman et al, 1997; Cannon et al, 2002).

Schizotypy is multidimensional and presents similarity to the symptom clusters in schizophrenia (Vollema et al, 1995). Therefore, schizotypal traits are evaluated in different dimensions such as, impoverished interpersonal relationships, oddities in perception, magical thinking, unusual speech, constricted affect, excessive social anxiety, suspiciousness, (Raine, 1991) paralleling the positive, negative and cognitive symptoms of schizophrenia. Thus, although there is no general agreement, three dimensions of schizotypy have been included in several studies: (i) a positive dimension, which includes symptoms such as magical ideation, ideas of reference,

and unusual perceptual experiences. (ii) a negative/interpersonal dimension which includes symptoms such as constricted affect, excessive social anxiety, no close friends, and (iii) a disorganized dimension, which includes symptoms such as odd speech, odd-eccentric behavior, (Bentall et al., 1989; Claridge et al., 1996; Raine et al., 1994; and Williams, 1994; Vollema, 2000; Kerns, 2006).

A two-factor model of schizotypy, corresponding to the positive and negative symptoms, which are found in schizophrenia (Kelley et al, 1992; Raine et al, 1989), has also been suggested. The schizotypes suffering from negative symptoms are characterized by social withdrawal and anhedonia, which may later develop into the negative symptoms of schizophrenia. Negative schizotypal symptoms are strongly associated with cognitive and neuropsychological deficits and are correlated with reduced dopaminergic neurotransmission in the prefrontal cortex. On the other hand, positive schizotypal symptoms are thought to possess idiosyncratic cognitive styles that may later develop into the positive symptoms (such as hallucinations and delusions) of schizophrenia. Positive Schizotypal symptoms are related to magical thinking, unusual experiences, odd behavior, and are associated with increased dopaminergic activity in subcortical mesolimbic structures just as schizophrenia is (Siever et al. 1993).

Chapter 4
Endophenotypes and Prepulse Inhibition of the Acoustic Startle Response

Endophenotypes are measurable, but not overtly observable, constructs in the pathway from genetic variation to psychiatric disorders. They are suggested to reflect the effects of genes predisposing an individual to a disorder, even in the absence of diagnosable pathology (Turetsky, 2007).

As originally conceptualized, an endophenotype:

- is associated with illness in the population.
- is heritable.
- is primarily state-independent, although it may need to be elicited by a challenge.
- is more prevalent among the ill relatives of ill probands compared with the well relatives of the ill probands (i.e., within families, endophenotype and illness cosegregate).
- is found in unaffected relatives of probands at a higher rate than in the general population.
- should be a trait that can be measured reliably and ideally is more strongly associated with the disease of interest than with other psychiatric conditions. (Gottesman et al, 2003; Chan et al, 2008).

Gottesman and Shields were the first to describe "endophenotypes", as internal phenotypes that could be discovered by a "biochemical test or microscopic examination (Gottesman, 1972; 1973). Quite often, the term "endophenotype" is mistaken for "biological markers", the "vulnerability markers" or "subclinical traits". However, an endophenotype must be cofamilial and heritable, whilst the other concepts do not imply or require either as a definitional criterion.

Studies have shown that endophenotypic deficits occur across the schizophrenia spectrum: in schizophrenia patients, schizotypal patients and clinically unaffected

relatives of schizophrenia patients (Cadenhead, 2000). Prepulse inhibition of the startle reflex, a stable neurobiological marker, with high reliability across repeated test sessions (Cadenhead et al, 1999; Braff et al, 2001) is one of the best neurophysiological endophenotypes studied in schizophrenia (Braff, 2005).

The startle reflex is an automatic contraction of the skeletal and facial muscles in response to a sudden and intense visual, auditory, or tactile stimulus. Prepulse inhibition of the startle response is a paradigm that provides an operational measure of the ability to screen out extraneous stimuli. This refers to the attenuation of the startle response, if a startling stimulus, the pulse, (e.g., a loud noise) is preceded, by around 30–500 ms, by a weaker stimulus, the prepulse, which is in the same or different sensory modality with the pulse (Graham, 1975) (Figure 1).

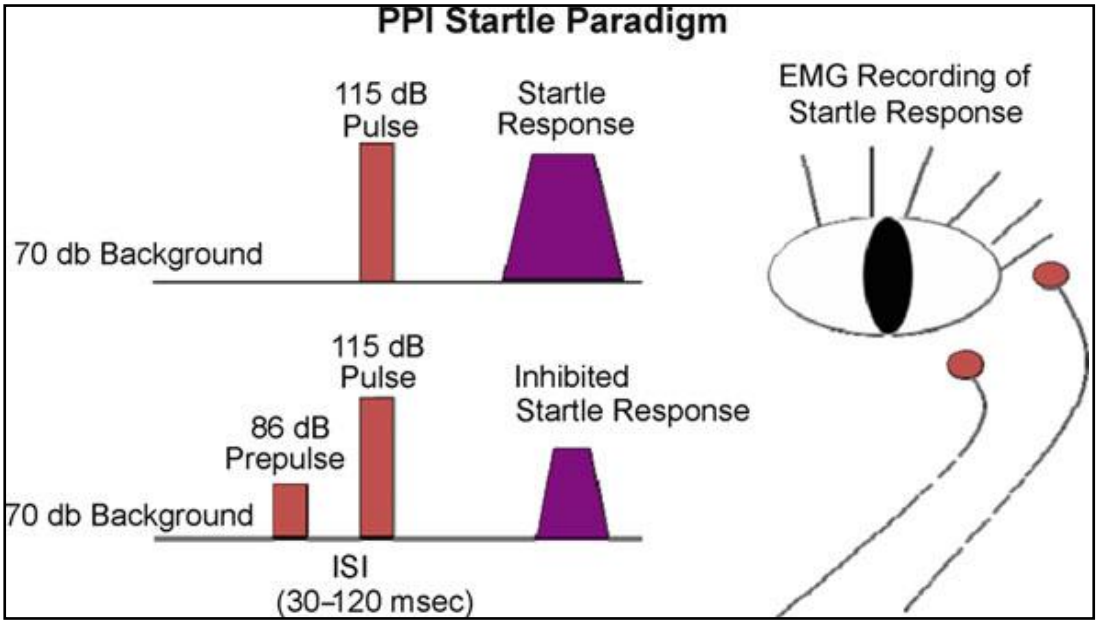

Figure 2.Prepulse Inhibition of the startle reflex (Swerdlow, 2010)

According to Graham's "protection of processing" theory (Graham, 1975) the onset of the prepulse initiates two automatic processes. The first process is trying to identify the lead stimulus and the second to protect the processing of the prepulse from interruption by the startle eliciting stimulus. Therefore, Prepulse inhibition is suggested to reflect "sensorimotor gating," whereby prepulses reduce the effect of

subsequent sensory stimuli to protect the brain from sensory overload (Graham, 1975).

Sensorimotor gating is conceptualized as a function helping the organism to regulate environmental inputs in order to navigate successfully in a stimulus-laden world full of non-salient stimuli, and to selectively allocate attentional resources to salient stimuli (Braff et al, 1978). From a neurobiological aspect, the prepulse exerts its inhibitory effects via a circuitry involving limbic and cortical regions, basal ganglia, and pons (Koch et al, 1997) (Figure 3). PPI reflects the activation of behavioral gating processes which are mediated by a forebrain neural circuitry and theories of the pathology of schizophrenia have implicated dysfunction in this circuitry (Swerdlow et al, 1987)

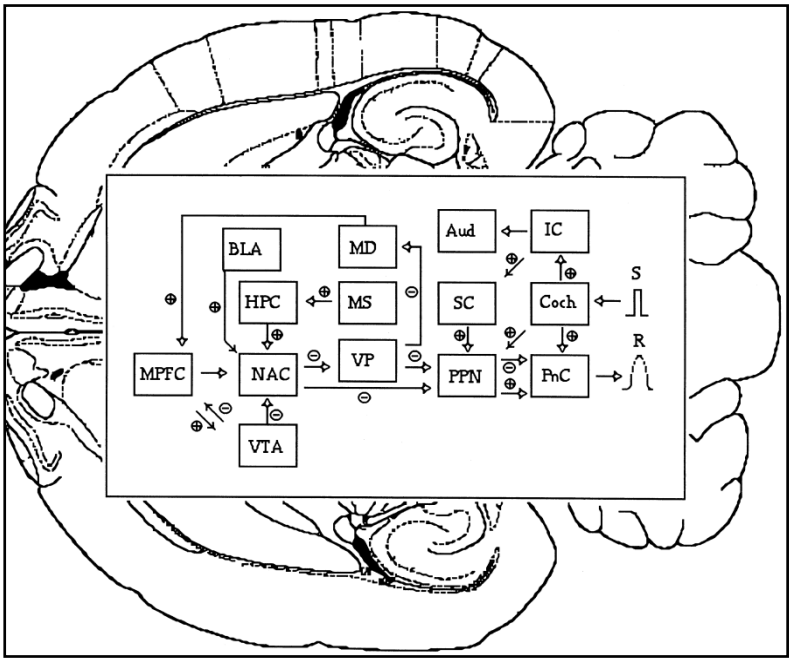

Figure 3.Model of neural substrates regulating acoustic startle and PPI in the rat. (Swerdlow, 2000)

Aud-auditory cortex, BLA-basolateral amygdala, Coch-cochlea, IC-inferiorColliculus, MPFC-medial prefrontal cortex, MS- medial septal nucleus, NAC-nucleus accumbens, MD-dorsomedial thalamus, PnC-nucleus reticularis pontis caudalis, SC- superior colliculus, VP-ventral pallidum, VTA-ventral tegmental area.

Specifically, PPI is mediated by a fast excitatory pathway, which is inhibited by a slower-activated parallel pathway. Both pathways converge at the level of the caudal pontine reticular nucleus (PNC), where the spinal motoneurons produce the startle response after acoustic stimulation. The excitatory pathway of the mediating circuit is composed of the cochlear root nucleus (CRN) that projects to the giant neurons in the caudal pontine reticular nucleus (PNC), whereas the inhibitory path includes the ventral (VCN) and dorsal cochlear nucleus (DCN), inferior (IC) and superior colliculi (SC), and the pendulopontine tegmental nucleus (PPT) (Laurrari et al, 2006) (Figure 4).

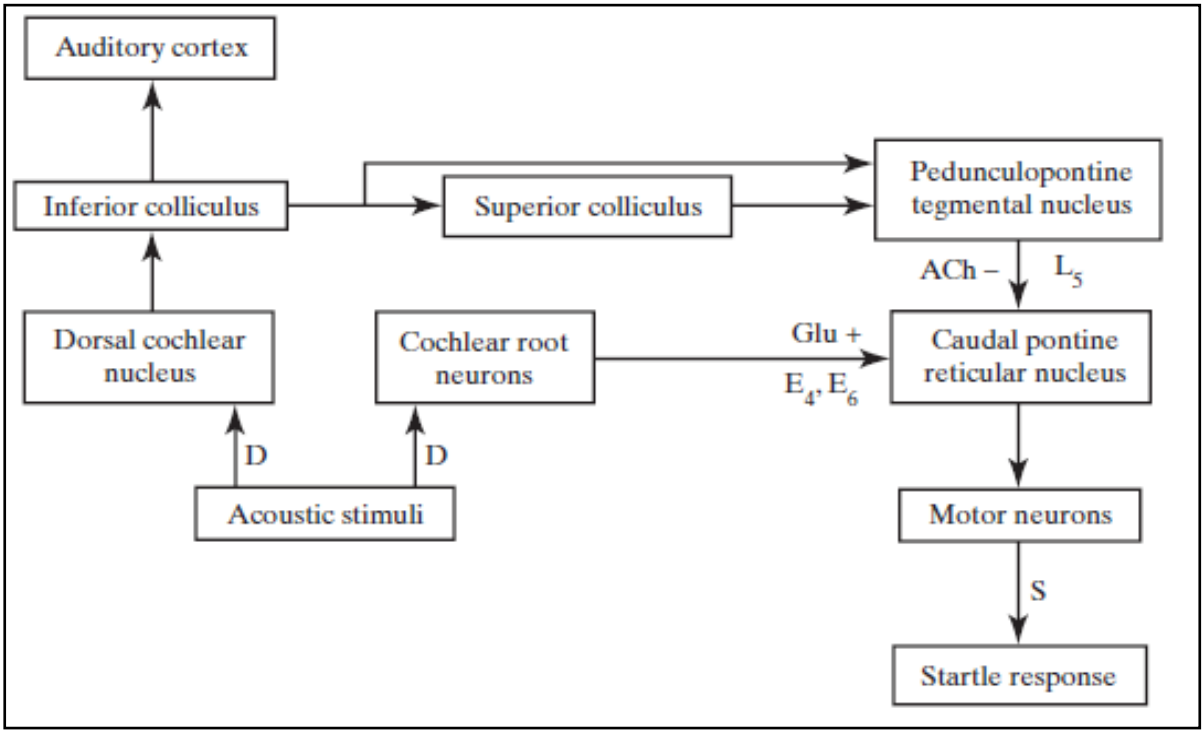

Figure 4.Excitatory and Inhibitory Pathways mediating startle response (Laurrari, 2006)

PPI is regulated by dopamine neurotransmission in the prefrontal cortex in a U shaped curve relationship between baseline PPI and PFC dopamine levels (Bitsios et al, 2005). PPI is reduced either when there is a decrease dopamine tone in medial prefrontal cortex or when there is an increase in DA activity in the region (Ellenbroek et al, 1996). D2 receptors have a primary role in PPI regulation (Caine et al, 1995), for example, PPI deficits occur after the blockade of D1 or D2 receptors in the

orbitofrontal cortex (Zavitsanou et al, 1999). Furthermore reduced PPI is observed after the infusion of DA agonists, such as apomorphine into the medial prefrontal cortex (Broersen et al, 1999).

Neuroimaging findings also support the important role of the prefrontal cortex in the regulation of PPI. In healthy individuals, greater PPI is associated with higher glucose metabolism (Positron Emission Tomography) in dorsolateral prefrontal cortex (DLPFC) regions (Hazlett et al, 2001) while in schizophrenia patients this relationship was observed in smaller portion of the prefrontal cortex (Hazlett et al, 2001). Moreover, functional magnetic resonance imaging (fMRI) performed in healthy individuals, showed increased blood oxygen-level dependent response in prefrontal cortex, thalamus, mediodorsal nucleus, and striatum during PPI modulation, while in schizophrenia patients there was a decreased activation in these regions (Kumari et al, 2003; Hazlett et al, 2001).

Braff et al, (1978) were the first to demonstrate that patients with schizophrenia have decreased PPI compared to normal controls. Non-medicated, non-psychotic schizotypal patients (Cadenhead et al, 1993) and clinically unaffected relatives of schizophrenia patients (Cadenhead et al, 2000) also show PPI deficits. The fact that PPI is deficient in schizophrenia, schizotypal patients and unaffected relatives, suggests that it may be a robust endophenotypic marker of psychosis.
PPI deficits and correlated cognitive abnormalities have been reported in schizophrenia patients (Bitsios et al, 2005) and across the "schizophrenia spectrum" of disorders from clinically unaffected relatives to schizotypal and prodromal schizophrenia patients. These patients are impaired in measures of sustained or "voluntary" attention and inability to automatically filter or "gate" irrelevant thoughts and sensory stimuli from intruding into conscious awareness (Cadenhead et al, 1993; 2000).

Chapter 5
The Neural Substrate of Schizotypy

Functional neuroimaging studies suggest that schizotypy is associated with neuronal mechanisms that are activated by tasks, the performance in which is an established neurocognitive marker of schizophrenia. The findings relating to the neural substrate of schizotypy are summarized in table 2.

Thus, individuals who scored high in positive schizotypy presented with reduced activation in the left dorsolateral prefrontal cortex and the nucleus accumbens, whilst elevated activation was found in the right dorsolateral prefrontal cortex, in the hippocampus and the amygdala (Mohanty et al, 2005) while performing a Stroop task. High schizotypy has also been associated with reduced activation in the putamen, cerebellum, thalamus, and visual cortex while the schizotypes were performing an oculomotor measure of executive function (Aichert et al, 2012). In addition, high schizotypal individuals showed significantly larger right prefrontal activation during a verbal fluency task, leading to more bilateral activation (Hori et al, 2008).

Cannon et al, (2002), tried to elucidate the dimensions of neuroanatomy that reflect the continuities and discontinuities between schizotypy and schizophrenia. Using magnetic resonance imaging of psychotic probands, their non-psychotic siblings and demographically matched controls, they found that patients and their siblings exhibited important reductions in frontal and temporal grey matter volumes and significant increases in frontal and temporal cerebrospinal (CSF) fluid volume. These findings suggest that the aforementioned deficits may be inherited.

Morphometric studies have also shown that individuals with high positive schizotypy had larger global volumes compared to subjects with low schizotypy, and larger regional volumes in the medial posterior cingulate cortex and the precuneus (Modinos et al, 2010). The reason for the greater volumes in these regions is not yet understood, but they may reflect functional compensation for early disturbances in other regions (Kawasaki et al. 2004). In another study, positive schizotypy was significantly

associated with reduced grey matter volume in medial prefrontal, orbitofrontal, and temporal cortical regions, thereby providing neurobiological evidence of a continuum between schizotypy and schizophrenia (Ettinger et al, 2011)

The relationship between cortical connectivity and schizotypy in the general population was assessed by Nelson et al, (2011). White matter integrity of the major association fibre tracts of healthy individuals with schizotypal traits was assessed using standard measures of diffusivity, specifically fractional anisotropy (FA) and axial and radial diffusivity. A variation in scores on the SPQ cognitive-perceptual factor was significantly predicted by median FA values in some major frontotemporal white matter tracts, such as the uncinate fasciculus, the temporal part of the right superior longitudinal fasciculus, and left cingulum. Decreased white matter integrity in these tracts was associated with positive anomalous experiences such as ideas of reference, odd beliefs, and magical thinking.

Chen et al, (2012) investigated whether the increased availability of striatal dopamine (DA) D2/3 receptors is related to elevated levels of schizotypal features in healthy individuals, using [^{123}I] iodobenzamide single photon emission computed tomography (SPECT) and the Schizotypal Personality Questionnaire (SPQ). This study was based on evidence of from previous studies on schizophrenia that supporting the view that the dopaminergic hyperactivity in the striatum is related to the positive symptoms of schizophrenia and brain-imaging studies of dopamine uptake in the striatum are thought to be linked to the pathophysiological mechanisms underlying the disease (Snyder, 1976). The SPQ disorganization subscale score was positively correlated with the availability of right striatal DA D2/3 receptors, but the SPQ total score showed no correlation with the availability of total (left and right) striatal DA D2 receptors.

Evidence links psychotic states and a hyperdopaminergic response to physiological or psychological stressors (Moore et al, 1999). Based on this finding Soliman et al, (2008), used positron emission tomography and [^{11}C]raclopride, to measure changes in synaptic dopamine concentrations in psychometric schizotypes with perceptual aberrations (PerAb, positive schizotypy) and with physical anhedonia (PhysAn,

negative schizotypy). Only the PhysAn group showed significant stress-induced dopamine release in the striatum. Furthermore, dopamine release in the entire sample was significantly negatively correlated with smooth pursuit gain, an endophenotypic measure linked to frontal lobe function. A possible neural basis for the striatal DA hyperreactivity in the PhysAn group is reduced frontal lobe function according to previous studies (Davis et al, 1991)

Table 2.Schizotypy and Neuroimaging studies.

Voxel Based Morphometry	
Modinos et al, 2010	Grey matter density increased in Medial Posterior Cingulate Cortex, Precuneus
Ettinger et al, 2011	Grey matter density reduced in Medial Prefrontal, Orbitofrontal, Temporal Cortical Regions
fMRI	
Mohanty et al, 2005.	Reduced activation of Left DLPFC, NAC. Increase activation of Right DLPFC, Hippocampus, Amygdala
Kumari et al, 2008.	Reduced activation of Inferior Frontal Gyrus, Insula, Parahippocampal Gyrus, Inferior Parietal and Temporal regions
Aichert et al, 2012.	Reduced activation of Putamen, Cerebellum, Thalamus, Visual Cortex
Cannon et al, 2002.	Volume of Frontal and Temporal Grey matter reduced. Volume of Cerebrospinal Fluid increased
Diffusion Tensor Imaging	
Nelson et al, 2010	Integrity of white matter decreased in frontotemporal regions
SPECT	
Chen et al , 2012	Increase of right striatal DA D2/3 receptors
PET	
Soliman et al, 2008	striatal DA hyperreactivity in the PhysAn group

Chapter 6
Schizotypy and Cognition

Increasing evidence suggests that psychometrically identified schizotypes from the general population have subtle cognitive impairments in several domains such as attention, working memory and executive functions. A lot of studies suggest that symptoms of schizophrenia and elevated schizotypal scores in healthy individuals are associated with similar disruptions in cognitive functioning. These studies are based on the theory of Claridge who proposes that the dimension of schizotypy lies on a continuum that begins with normality and proceeds towards the schizophrenia spectrum disorders, with schizophrenia at the upper end (Claridge et al, 1995).

6.1 Executive functions

Executive functions are a collection of processes that are responsible for guiding, directing, and managing cognitive, emotional, and behavioral functions, particularly during active, novel problem solving (Gioia et al, 2000). Executive functions according to Lezak, are comprised by four components: (1) volition; (2) planning; (3) purposive action; and (4) effective performance (Lezak et al, 2004). An individual suffering from executive dysfunctions may manifest serious problems in everyday life, regarding inappropriate social behavior, problems with decision making and showing good judgment, difficulties with devising, following, and shifting plans, problems with organization, distractibility and difficulties in situations involving various aspects of memory (Gioia et al, 2000).

6.1.1 Verbal fluency

Verbal fluency (VF) is a common test of response generation and has been suggested to be a cognitive phenotype as it is impaired in schizophrenia patients (Liddle et al, 1991), their unaffected siblings (Franke et al, 1993) and in patients with schizotypal

personality disorder (SPD) (Diforio et al, 2000). Verbal fluency is thought to reflect executive functioning, such as cognitive switching, rule monitoring, and inhibition of inappropriate responses.

Negative schizotypy has been found to be positively associated with VF deficits in unaffected siblings of schizophrenic patients (Franke et al, 1993), while an association between reduced verbal fluency and high schizotypy in healthy individuals has also been reported (Cochrane et al, 2012; Tsakanikos et al, 2005).

6.1.2 Wisconsin Card Sorting Test

Wisconsin Card Sorting Test (WCST) is used as a measure of 'executive' or higher-order cognitive functions such as working memory, abstraction, maintenance of set, and response to feedback (Lezak, 1995) and taps neuropsychological processes involving (a) cognitive flexibility, (b) problem-solving, and (c) response maintenance (Greve et al., 2002). Patients suffering from schizophrenia complete fewer categories and make more perseverative errors than the normal controls (Gold et al, 1997). Performance in the task has been correlated with the negative symptoms of schizophrenia (Breier et al, 1991).

Across the schizophrenia spectrum, poor performance in the WCST has also been shown in unaffected first degree relatives of schizophrenia patients and individuals suffering from schizotypal personality disorder. Unaffected first degree relatives of schizophrenics showed worse performance in the WCST in comparison with healthy controls in the studies of Pogue-Geile et al, (1991) and Hamaoui et al, (2006). Laurent et al, (2001) found that a subgroup of relatives of schizophrenia patients with high scores on the negative dimension of schizotypy (Chapman's Scales) showed worse performance in the WCST than the subgroup with low scores. Moreover, healthy siblings of schizophrenic probands revealed more perseverative responses than healthy controls (Franke et al, 1992; Diwadkar et al, 2006). Patients suffering from Schizotypal personality disorder have also poorer performance in the WCST than healthy controls (Minzenberg et al, 2006; Voglmaier et al, 1997; Trestman et al, 1995).

Apart from unaffected first degree relatives of schizophrenia patients and people suffering from SPD, poor performance in the WCST is also shown for healthy individuals with high scores on scales assessing schizotypy. Raine et al, (1992), using the WCST and magnetic resonance imaging found that high schizotypal individuals from the general population had reduced prefrontal activation and more WCST perseveration errors. Furthermore, Lenzenweger et al, (1994) showed that individuals with high scores on the perceptual aberration scale (indicative of positive schizotypy) complete less WCST categories and they also fail to maintain set and produce higher perseverative errors. This pattern in performance has been observed in other studies as well (Gooding et al, 1999; Kim et al, 2011).

6.1.3 Stroop Colour and Word Test

The Stroop interference test requires the subject to inhibit the response to the semantic value of the word and attend to the color content and schizophrenic patients present with longer reaction times compared with controls (Barch et al, 2004). Westerhausen et al, (2011) in a meta-analytic study on the Stroop interference effect and schizophrenia, concluded that schizophrenia patients exhibit
increased Stroop interference effect both in response time and accuracy measures of interference (Westerhausen et al, 2011). First degree relatives of schizophrenia patients demonstrate disproportionately increased slowness on the Stroop test (Zalla et al, 2004) and perform worse in comparison to normal healthy individuals (Breton et al, 2011; Szoke et al, 2005). Research findings in patients with schizotypal personality disorder are not clear as studies do not present significant results regarding the performance of SPD patients in the task (Cadenhead et al, 1999; Trestman et al, 1995; Mitropoulou et al, 2005).
However, healthy individuals with high scores in schizotypy scales perform poor in the Stroop test. In more detail, Cimino et al, (2008) assessed the performance of people scoring high and low on the O-LIFE (Oxford-Liverpool Inventory of Feelings and Experiences) schizotypy scale in a Stroop-like switching task. It was shown that high schizotypes were slower and less accurate than low schizotypes in all conditions, including the congruent condition. Steel et al, (1996), also tested healthy individuals, who scored high in the O-LIFE schizotypy questionnaire and found that high

schizotypes displayed slower response times compared with low schizotypes. Swerdlow et al, (1995), categorized their sample into "psychosis prone" and "normal group", according to MMPI criteria and tested them with Stroop and PPI. PPI was significantly reduced in the group of psychosis-prone subjects who they also performed worse than controls in the interference task.

6.1.4 Iowa Gambling Task

The Iowa Gambling task is an index of emotion based decision making, i.e. the ability to modulate the reward and punishment perception, in order to make advantageous choices. The Task was developed according to the Somatic Marker Hypothesis of Damasio and was initially designed to capture the role of the orbital frontal cortex in risk taking in patients with frontal lobe damage (Damasio, 1996; Bechara et al, 1994). Apart from adults with VmPFC damage, there are also some other groups who perform poorly on the task, including people who abuse substances, such as drugs and alcohol (Bechara et al, 1994; Bechara et al, 2001), patients with neurological and psychiatric disorders, such as ADHD, pathological gamblers, and schizophrenics (Kester et al, 2006; Toplac et al, 2005; Toplac et al, 2007).
Impaired performance on the task has been found not only in chronic schizophrenia patients (Fond et al, 2012; Kim et al, 2009), but also in adolescents with early-onset schizophrenia (Kester et al, 2006). Furthermore, positive symptoms have been associated negatively with the net score on the IGT, (Struglia et al, 2011).

So far, there are no findings on the effects of schizotypy on IGT performance.

6.2 Memory

Memory refers to the complex processes by which the individual encodes, stores, and retrieves information. According to Moscovitch, (2004), memory is comprised of a variety of different forms. Each form is mediated by different processes and different neural substrates. Memory can be divided, in respect to temporal characteristics, into short term and long term**.** Long-term memory refers to the permanent or more stable

storage of memories, while short term memory, also known as working memory, is conceived of as a limited-capacity store for retaining information over the short term (seconds to 1–2 minutes) and for performing mental operations on the contents of this store. The two major categories of long term memory are the conscious or explicit memory and the unconscious or implicit memory. Explicit memory is further divided into episodic memory, or memory for personal experiences, and semantic memory, or memory for facts. Implicit memory can be divided into motor memory, priming, and classical conditioning, (Strauss, Oxford University Press, 3rd edition, 2006)

Fioravanti et al, (2005), performed a meta-analysis examining cognitive deficits of schizophrenia patients in 5 different domains: Memory functioning, Global cognitive functioning, Language, Executive functions and Attention. According to the measures of memory functioning, there is a significant decline among the patients with schizophrenia, confirmed by the high probability (81%) to find a patient with memory impairment. Global deficits in declarative memory are commonly reported in individuals with schizophrenia and in their biological relatives (Stefanopoulou et al, 2009; Sitskoorn et al, 2004; Toomey et al, 1998; Giakoumaki et al, 2011). Therefore, working memory deficits are proposed as potential endophenotypes for schizophrenia.

Studies examining the effects of schizotypy on memory, showed that students, who scored high on the Chapman Perceptual Aberration Scale, performed less accurately compared with the low perceptual aberration controls on the delayed-response task (assessing spatial working memory) and they were more than twice as likely as low PerAb students to be impaired (Park et al, 1995). Also, individuals scoring high on the Social Anhedonia and Perceptual Aberration Scales displayed poorer performance and slower reaction times than the control group on working memory tasks, (Tallent, 1999; Kerns et al, 2008). Reduced working memory performance has also been found in participants who displayed high levels of positive schizotypy and, to some extent, in participants with low levels of negative schizotypy (Schmidt, 2009).

In the study of Bo-Yeon Song et al, (2011), explicit and implicit memory of nonclinical individuals with schizotypal traits (SPQ scale) using event-related potentials was investigated. They found that individuals with schizotypal traits have

impaired explicit but preserved implicit memory, a finding that is also true for schizophrenia patients (Bozikas et al, 2006; Besche-Richard et al, 2005).

Wang et al, (2008), explored the memory profiles of schizophrenic and psychometrically defined schizotypal subjects. The participants completed verbal and visual memory, working memory, and prospective memory tasks. The results showed that patients with schizophrenia were impaired in all aspects of memory function, whereas the schizotypal subjects tended to show moderate to large impairment effect sizes in prospective memory.

6.3 Attention

Attention refers to one's ability to detect the signal in complex incoming sensory information. It consists of several basic processes, such as sensory selection (filtering, focusing, automatic shifting), response selection (response intention, initiation and inhibition, active switching, and executive supervisory control), attentional capacity (structural and energetic capacity, arousal, effort), and sustained performance (fatigability, vigilance), (Cohen, 1993). Attention is divided into focused, selective, divided and sustained attention.

Sustained attention deficits have been associated with schizophrenia as they are consistently found in different stages of the illness and in non-psychotic first-degree relatives of patients with schizophrenia, (Egan et al, 2000; Sitskoorn et al, 2004; Franke et al, 1994). Many studies use Continuous Performance Tasks (CPT) to examine sustained attention. These studies have found that psychosis prone individuals (based on elevated scores on the Chapman Perceptual Aberration and on the Social Anhedonia Scale or on STA and PAS schizotypy measures) performed poorly compared with controls in terms of discrimination ability (Gooding et al, 2006) and omission errors (Obiols et al, 1993) while increased random errors were related to increased reality distortion (Bergida et al, 2006). Poorer performance in another sustained attention task (the Sustained Attention Response to Task) has also been reported in high schizotypal individuals (Raymond et al, 2009).

Regarding Selective attention, Breeze et al, (2011) found that high-schizotypy subjects consistently showed increased switch costs in the tasks demonstrating a deficit in the selection of the perceptual dimension instead of the selection of the response rules.

Chapter 7
Schizotypy and Prepulse Inhibition of the Acoustic Startle Response

Examining PPI of psychometrically identified high-risk healthy populations is again based on the hypothesis that proneness to psychosis may constitute a personality trait that lies on a continuum and schizophrenia is conceptualized as the end of it (Claridge, 1973). However, research findings regarding the correlation of schizotypal traits and deficiency of the prepulse inhibition of the startle reflex are controversial.

Many researchers provide evidence, which support the view that PPI is deficient, not only in schizophrenia patients (Braff et al. 1978; Weike et al. 2000), but also in schizotypal patients who do not suffer from psychosis (Cadenhead et al. 1993). Moreover, PPI has been found to be deficient in unaffected first-degree relatives of schizophrenia patients (Cadenhead et al. 2000). These findings make PPI an important endophenotype (Braff et al, 2001).

A good number of studies have shown that healthy individuals from the general population, who score high in schizotypy scales also present with PPI deficits. Specifically, Simons et al, (1992) found that individuals scoring high on the perceptual aberration scale (of the Chapman's Scales) showed reduced PPI compared with controls and similar results have also been reported in another study using the Chapman's Scales (Schell et al, 1995) and in studies using different psychometric scales such as the MMPI (Swerdlow et al 1995), the Eysenck Psychotism Scale of the Eysenck Personality Questionnaire (Kumari et al., 2008) and the Schizotypal Personality Questionnaire (Takahashi et al., 2010).
However, the relationship between schizotypy and PPI is not clear enough, as other studies have shown that there is not a difference in PPI between healthy controls and individuals scoring high in schizotypy scales. For example, Perlstein et al, (1989) showed that individuals scoring high on the perceptual aberration scale demonstrated normal prepulse inhibition and analogous findings were also reported by Cadenhead

et al, (1992), Blumenthal et al, (1994), Weike et al, (2001), Evans et al, (2005), and Abel et al, (2004).

Some possible explanations for the inconsistency of the results could be methodological limitations, such as small sample size, the effect of the smoking status of the participants on the PPI, the effect of the women's menstrual phase on PPI, and the use of different sample exclusion criteria by each study. Specifically, the study of Abel et al, (2004) included only 44 participants, the study of Weike et al, (2001) included 32 participants, while the study of Kumari et al, (2008) included only 14 participants; the rest of the studies had a sample of over 64 participants. This is a significant methodological issue, as a small number of the participants does not give the power required to detect possible associations. The smoking status of the participants is another important factor because plenty of studies have demonstrated that healthy individuals and schizophrenics have enhanced PPI after smoking a cigarette (Kumari et al, 1996; Kumari et al, 1997; Della Casa et al, 1998). However, most of the aforementioned studies do not take into consideration the smoking status of their subjects (Simons et al, 1992; Swerdlow et al, 1995; Schell et al, 1995; Blumenthal et al, 1994; Weike et al, 2001; Abel et al, 2004). Furthermore, while in most of the studies women were overpresented in the sample, their menstrual phase was not evaluated. Healthy women show less PPI compared with men, and this varies according to their menstrual cycle phase (Kumari et al, 2010; Jovanovic et al, 2004; Swerdlow et al, 1997).

Aim of the Present Study

Based on the above and given that the differential aspects (positive vs. negative) of schizotypy have not been adequately studied, the aim of the present study is to examine the effects of psychometrically identified positive and negative schizotypy on PPI of the acoustic startle response and on cognitive functions in the general population. Consistent with the literature, it is hypothesized that high positive or negative schizotypal participants will show deficient PPI and poorer performance in the neuropsychological tasks in comparison with the low schizotypal participants.

Part B’
Methodology

Chapter 8
Materials and Methods

8.1 Subjects

Two-hundred and thirty five healthy males aged 20.75 ±02.58 (mean ±SD, age range: 18-30) participated in the study. We restricted the sample to men to avoid PPI variability related to gender (Swerdlow et al, 1993) and menstrual cycle (Swerdlow et al, 1997).Inclusion criteria were: right-handedness, absence of personal history of head trauma, absence of medical and neurological conditions, or use of prescribed and recreational drugs, absence of personal or family (up to first-degree relatives) history of DSM-IV Axis I disorders and hearing threshold greater than 40 dB at 1 kHz. All subjects underwent psychiatric assessment using the Mini-International Neuropsychiatric Interview (Sheehan et al, 1998). IQ was estimated with the Raven's Standard Progressive Matrices. One-hundred and forty five subjects were smokers and ninety were non-smokers. All subjects were regular caffeine and occasional social alcohol consumers. The study was approved by the Ethics Committee of the University of Crete and all subjects gave their written informed consent after description of the study, prior to enrollment.

8.2 Startle and PPI measurements

A commercially available electromyographic startle system (EMG SR-HLAB, San Diego Instruments, San Diego, CA, USA) was used to examine the eyeblink component of the acoustic startle response. Acoustic stimuli were administered binaurally through headphones (model TDH-39-P, Maico Minneapolis, MN). Electromyographic recordings (EMG) were taken while subjects were seated comfortably in an armchair, instructed to relax and stay awake. The eyeblink component of the startle reflex was indexed by recording EMG activity of the orbicularis oculi muscle directly beneath the right eye, by positioning two miniature

silver/silver chloride electrodes filled with Signa gel electrolyte paste (Parker Laboratories Inc., New Jersey, USA). The ground electrode was attached behind the right ear on the mastoid. Resistance was kept lower than 10 kΩ. EMG activity was band-pass filtered (100–1000 Hz) and a 50-Hz filter was used to eliminate the 50 Hz interference.

Pulses consisted of 40-ms, 115-dB white noise bursts, and prepulses consisted of 20-ms, 75-dB and 85-dB white noise bursts over 70-dB background noise. Recording began with 3 min of acclimation when only background noise was present. The recording period comprised 12 pulse-alone trials and 36 prepulse–pulse trials. Three lead intervals were used (30, 60, 120 msec). All trials were presented in pseudorandom order with the constraint that no two identical trials occurred in succession. The inter-trial interval varied between 9 and 23 sec (average 15 sec). The entire test session lasted approximately 15 min.

Before scoring and data analysis, all recordings were screened for spontaneous eyeblink activity. Trials were excluded, if excessive EMG activity (> 20 digital units) was observed during the first 20 msec of recording or when onset latencies (defined by a shift of 20 digital units from the baseline value, occurring within 20–85 msec after the onset of the pulse stimulus) and peak latencies (the point of maximal amplitude) differed by more than 95 msec. Any subject missing more than two (out of six) prepulse-pulse trials per trial type and/or more than two (out of twelve) pulse-alone trials was discarded. The maximum absolute amplitude of the raw EMG data occurring in the 20–150 time window of the non-rejected trials was scored offline and stored for averaging and data analysis. The maximum amplitudes of the raw EMG responses from each trial were averaged across all trials of the same type, and percentage prepulse inhibition (% PPI) was calculated using the formula $[(\text{Amplitude}_{\text{Pulse-alone}} - \text{Amplitude}_{\text{Prepulse-pulse}})/\text{Amplitude}_{\text{Pulse-alone}}] \times 100$.

8.3 Neuropsychological Assessment

8.3.1 Stroop Interference Test (SIT)

The Stroop Test is an "interference" task because it requires the subject to inhibit the response to the semantic value of the word and to attend to its color content. The standardized version of this test was used (Golden, 1978). Subjects read for 45 sec from a standardized list of words, "blue," "green," or "red," written in black ink and presented in random order. The number of words correctly read in the 45-sec period was recorded ("word score"). Next, subjects named the color of patterns within a standardized list of blue, green, or red-colored patterns, presented in random order, and the number of colors correctly identified in that 45-sec period was recorded ("color score"). Finally, subjects identified the color of the ink that was mismatched to a word (e.g., the word "red" printed in blue ink is identified as "blue"), and the number of correct responses in that 45-sec period was recorded ("colour-word score"). Interference scores are calculated using the formula Color Word – Color Word′, where Color Word′ is the “predicted number of words”, the subject “could” name in the Color Word condition, and is derived from (Word × Color)/(Word + Color) = Color Word′.

8.3.2 Verbal Fluency Controlled Oral Word Association Test (COWAT)

A Greek version (Kosmidis et al, 2004) of the task was used. The task is comprised of three semantic and three phonemic categories. On the semantic part, participants have to generate as many different words as possible, belonging to each of the following three semantic categories: animals, fruit, and objects, for one minute per category. On the phonemic part, participants have to generate as many different words as possible, beginning with each of the following three Greek letters: X (Chi), S (Sigma), and A (Alpha), for one minute per letter. The total number of correct responses generated was calculated for the semantic and phonemic parts separately. The number of clusters generated in the phonemic (successively generated words that begin with the

same first two letters, words differing only by a vowel sound) and the semantic (successively generated words belonging to the same semantic subcategories) parts were calculated. Switches were also calculated as the number of transitions between clusters, including single words. Repetition (generating the same word more than once) and intrusion (any unrelated word/condition) errors were also recorded.

8.3.3 Wisconsin Card Sorting Test (WCST)

A computerized version of the WCST (Harris, 1988) was administered. The task consisted of four stimulus cards that varied along three dimensions (colour, shape, and number). Participants were given 36 cards that varied along the same dimensions and were asked to match the cards in the deck with one stimulus card. The computer screen displayed 'Right' for the correct placements and 'Wrong' for the incorrect, but did not reveal the sorting strategy. Once six consecutive cards were categorized correctly, the sorting principle changed. We used a modified version of the task, as suggested by Nelson (1976), so that the examiner tells the subject when the matching principle changes to reduce potential distress. The main outcome variables included the number of categories completed, number of Milner Type perseverative errors (errors made on the immediately preceding stage of the test) (Milner, 1963), Nelson Type perseverative errors (all other perseverative errors) (Nelson, 1976), and total number of errors.

8.3.4 N-Back Sequential Letter Task

The task consisted of four conditions (0-, 1-, 2-, and 3-back). Subjects were asked to respond by a button press when they saw a target letter (letter "X" for 0-back and any letter that was identical to the one presented in the preceding 1, 2, or 3 trials, respectively) on the computer screen. The outcome variables were the number of correct responses and the number of false alarms (giving a response when no target-stimulus was present).

8.3.5 Iowa Gambling Task (IGT)

Participants were instructed to select one card at a time from four decks (A, B, C, D) displayed on the screen in order to win pretend money. Unknown to the subjects, decks A and B were associated with high monetary rewards but also high penalties (monetary loses) while decks C and D had lower rewards but also lower penalties. The win or loss associated with the selection of a card appeared visually on the screen. Across 100 trials, more choices from the decks C and D lead to a net gain while choosing from the other two decks resulted in greater loss. Dividing card selections into 5 blocks of 20 allowed us to determine the rate of learning over the course of the task. Scores were (i) total numbers of cards selected from advantageous decks C and D minus total numbers of cards selected from "risky" decks A and B, with a higher score indicating superior performance (ii) total money won and (iii) overall learning defined as the difference between block 5 and block 1 in the number of advantageous minus disadvantageous card selections.

8.3.6 Word Lists

We used the Word Lists subtest of the Weschler Memory Scale (WMS-III) from the WAIS-R (Weschsler, 1997), to assess verbal learning and memory. A list of 12 words was read, and subjects were asked to recall the words in any order (immediate recall); this procedure was repeated four times. After Trial 4, an interference trial with a new list occurred, and subjects were subsequently asked to recall as many words as possible from the first list (short-delay recall). Thirty minutes later, subjects were asked to recall the words from the first list again (long-delay recall). The test finished with a recognition memory trial: a list of words was read, and subjects were asked to identify the words included in the first list (recognition). Outcome variables were the number of correct responses per recall condition (immediate four trials, short delay, long delay) and intrusion errors (words identified that were not included in the list).

8.3.7 Cambridge Neuropsychological Test Automated Batteries (CANTAB)

Cambridge Neuropsychological Test Automated Battery (CANTAB) is a set of neuropsychological test batteries developed by Morris et al, (1986) and standardised in a large group of normal subjects (Robbins et al, 1994; 1998). The tasks included are nonverbal, administered with the aid of a high-resolution touch-sensitive screen (Advantech), with continuous and sensitive adjustment of levels of difficulty, obviating floor and ceiling effects. The CANTAB tests employed were:

8.3.7.1 Stockings of Cambridge (SoC, Figure 5)

Subjects were asked to rearrange with the minimum possible number of moves, *balls* presented in *socks* in the lower half of the screen such that their positions matched a target arrangement in the upper half. The test presents the subject with easy 2- and 3-move and harder 4- and 5-move problems. Subjects are asked to plan the complete sequence of moves required to solve the problem prior to their first move. Initial thinking time (ITT) prior to execution of the first move, subsequent thinking time (STT) for the execution of all subsequent moves, and problems solved in minimum moves are recorded. Poor performance in this test translates into shorter ITT (less time planning), and/or longer STT (more time executing the solution) with less perfect solutions.

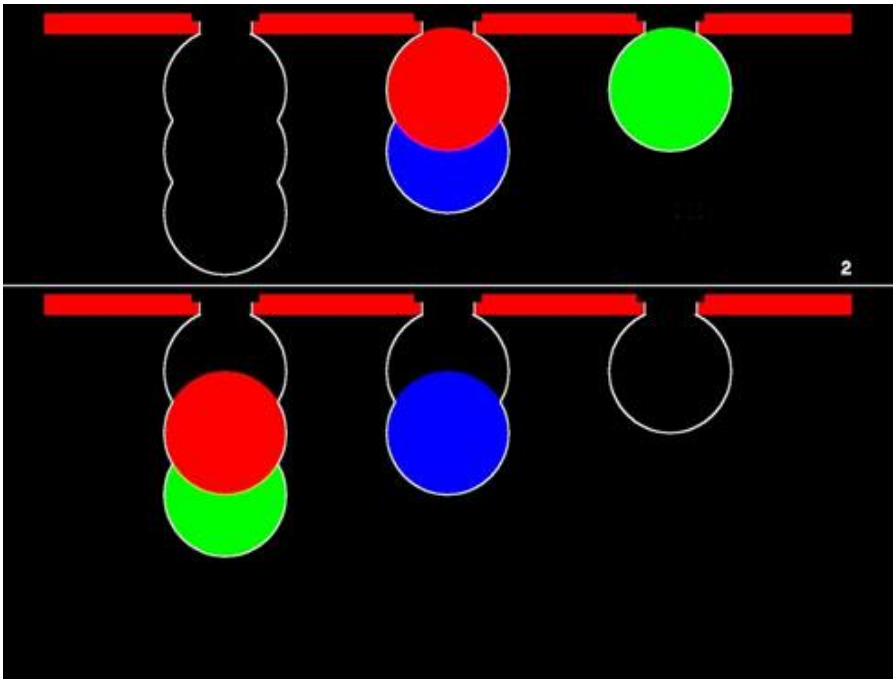

Figure 5.Stockings of Cambridge, Copyright®_ Cambridge Cognition, UK

8.3.7.2 Spatial Working Memory (SWM, Figure 6)

The SWM tests spatial working memory and spatial strategy. Subjects are required to search through an increasing number (two, four, six, eight) of boxes, randomly arranged on the screen, until they find a single token that, at any one time, is hidden in one of the boxes. The key instruction is that once a token has been found within a particular box, that box should never be used again to hide a token. On each trial, every box is used once to hide a token such that the total number of tokens to be found corresponded to the number of boxes on the screen. Errors are scored according to the number of occasions on which a subject returns to open a box in which a token has already been found. An efficient strategy for completing this task is to follow a predetermined search sequence, beginning with a particular box and then returning to start each new sequence with that same box as soon as a token has been found. The extent to which this repetitive searching pattern is used as a strategy for approaching the problem, is estimated from the number of search sequences starting with the same box, within each of the more difficult 6- and 8-box problems. The total of these scores provides a single measure of strategy for each subject, with a high score (many

sequences beginning with a different box) representing low use of the strategy and vice versa.

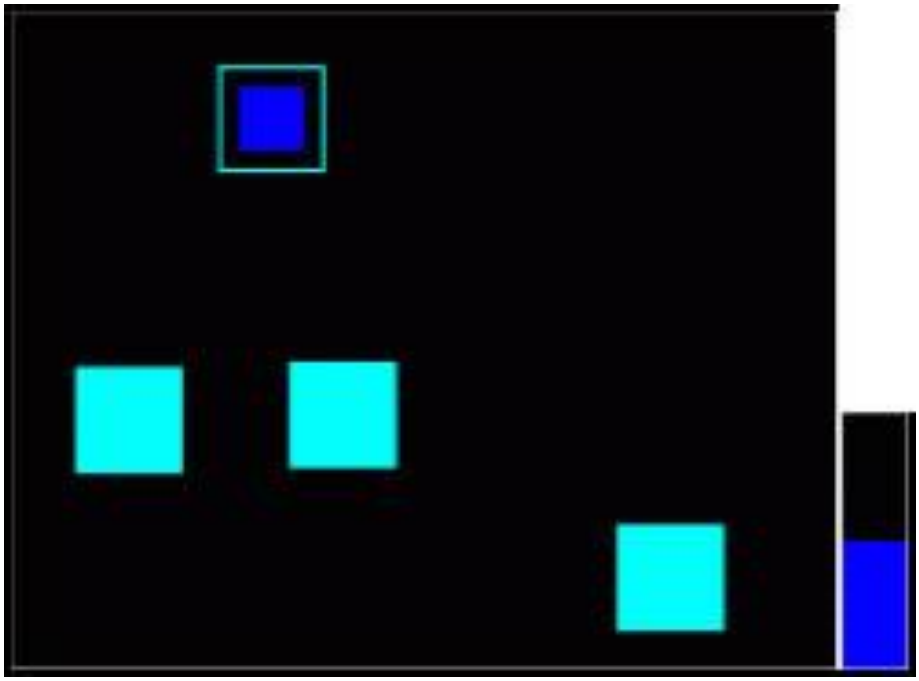

Figure 6 Spatial Working Memory Copyright®_ Cambridge Cognition,UK

8.3.7.3 Rapid visual information processing (RVIP,

8.3.7.4Figure 7.Rapid visual information processing Copyright®_ Cambridge Cognition,UK

8.3.7.5)

Subjects were asked to detect consecutive target sequences of digits (e.g. the sequence 3-5-7) presented at the rate of 100 digits per minute for four minutes and responses were registered by a button press. Main performance measures included: total hits (number of targets correctly detected), total misses (number of undetected targets), and total false alarms (number of responses made in the absence of targets). From these, calculations of sensitivity (A′: tendency to detect target sequences) and response bias (B′: tendency to respond regardless of target sequence) are possible, derived from Signal Detection Theory (Sahgal, 1987; Swets, 1996) which take both hit probability and false alarms into consideration.

Figure 7.Rapid visual information processing Copyright®_ Cambridge Cognition,UK

8.3.7.6 Reaction Time (RTI, Figure 8)

The 5-choice RTI measures visual attention (Chari et al, 1996). Subjects must release a home button (reaction time) and then touch whichever of five target stimuli has been indicated on the touch-screen (movement time). Outcome measures used were 5-choice reaction (i.e. the time taken to release the home button) and movement latencies (i.e. the time taken from button release to screen touch).

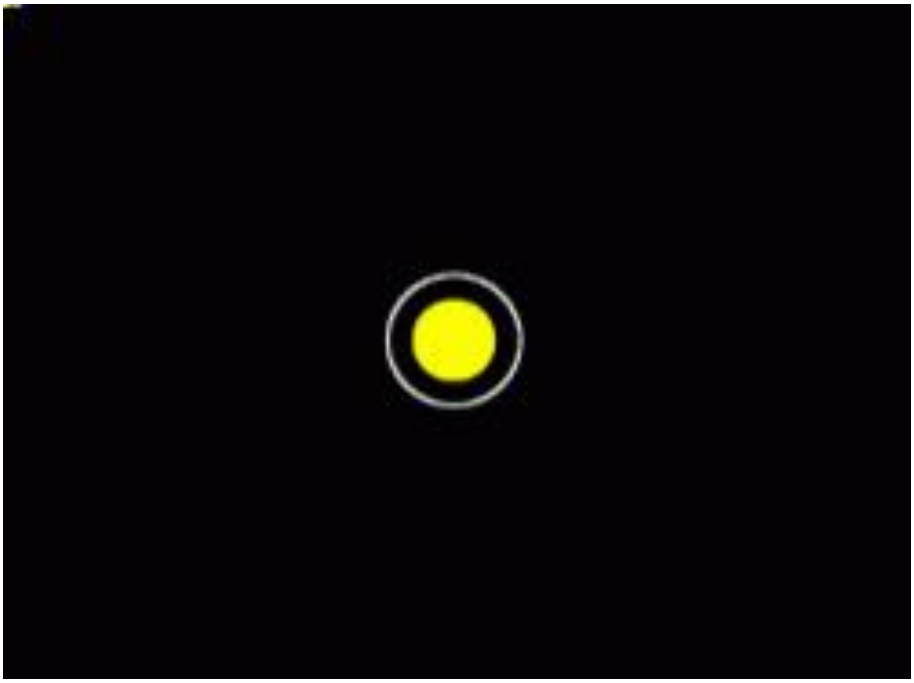

Figure 8 Reaction Time, Copyright®_ Cambridge Cognition,UK

8.3.7.7 Paired Associates Learning (PAL, Figure 9)

The PAL test assesses episodic memory and learning (Blackwell et al, 2004). It consists of eight stages; in each stage, boxes are displayed on the screen, and open in randomized order. One or more boxes contain a pattern. The patterns shown in the boxes are then displayed in the center of the screen, one at a time, and the participant has to touch the box where the pattern was originally located. Three target indices were included: (1) total errors (2) total trials required to locate all the patterns correctly in all stages and (3) first trial memory scores.

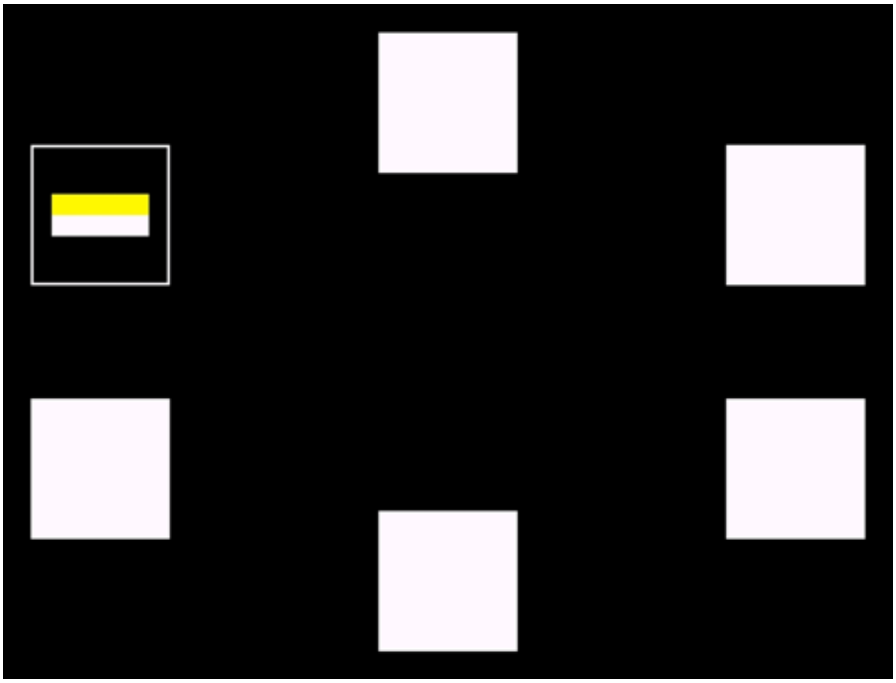

Figure 9 Paired associate learning, Copyright®_ Cambridge Cognition,UK

8.4 Personality Assessment

8.4.1 Schizotypal Personality Questionnaire (SPQ)

Schizotypal personality traits were assessed with the, Schizotypal Personality Questionnaire (SPQ) (Raine, 1991). SPQ is a self-report scale with 74 yes/no questions, comprising nine subscales, based on the diagnostic criteria for schizotypal personality disorder. These subscales include ideas of reference, magical thinking, unusual perceptual experiences, suspiciousness/paranoia, social anxiety, eccentric behaviour, disorganised speech, few close friends, and constricted affect. Factor analyses of the SPQ items have indicated three major factors (Raine et al, 1994): positive, negative and disorganized features, paralleling the three-syndrome model of schizophrenia (Liddle, 1987).

8.4.2 Cloninger's Temperament and Character Inventory (TCI)

TCI was developed by the psychiatrist Robert Cloninger (Cloninger, 1987; 1993; 1994) and is based on his psychobiological theory of personality. It distinguishes between Temperament and Character Dimensions. The Temperament Dimensions are based on the hypothesis that neurochemical transmitters (serotonin for the behavioural inhibition system, dopamine for the activation system, noradrenalin for the behavioural maintenance system) determine the stable stimulus—response patterns which underlie personality traits. According to the phylogenetic development of temperament, Cloninger et al. (1993) identified the following Temperament Dimensions: (i) a behavioural inhibition subsystem underlying harm avoidance (pessimistic worrying in anticipation of problems), (ii) an activation subsystem underlying novelty seeking (the initiation of the appetitive approach in response to novelty), (iii) a behavioural maintenance subsystem underlying reward dependence (the maintenance of behaviour in response to cues of social reward), and (iv) an additional independent dimension: persistence (perseverance despite frustration and fatigue). The Character Dimensions refer to self-concepts and individual differences in goals and values, which influence voluntary choices, intentions, the meaning and salience of what is experienced in life. The three Character Dimensions are Self-Directedness, Cooperativeness, and Self-Transcendence. TCI consists of 120 items answered in a dichotomous (true/false format).

8.4.3 Symptom Check List (SCL-90-R)

The SCL-90-R is a 90-item self-report symptom inventory developed by Derogatis, (1977) and designed to screen for a broad range of psychological problems. Each of the 90 items is rated on a five-point Likert scale of distress, ranging from ``not at all'' (0) to ``extremely'' (4). Answers are categorized into nine primary symptom dimensions: Somatization, Obsessive-Compulsive, Interpersonal Sensitivity, Hostility, Depression, Anxiety, Paranoid Ideation, Phobic Anxiety and Psychoticism. In addition, three global indices provide measures of overall psychological distress: the Global Severity Index (GSI), the Positive Symptom Total (PST) and the Positive Symptom Distress Index (PSDI).

8.5 Statistical analyses

All variables from the neuropsychological tasks were subjected to a Principal Component Analysis (PCA) using the varimax rotation method; components with Eigenvalues >1 and factor loadings >0.4 were accepted. Scores were Z-transformed and summed to generate cognitive factor scores. Pearson correlations between subjects, demographic variables, SPQ scores and the retrieved cognitive factors were conducted. Following this, we examined associations of each cognitive factor with "Positive" and "Negative" subscale scores of the SPQ in the entire sample, with a series of univariate regression analyses (dependent variable: cognitive factor; independent variables: Positive, Negative or Total Schizotypy score, age, number of cigarettes smoked/day). These analyses were conducted assuming a p=0.050 significance level and a two-sided alternative hypothesis.

We stratified our subjects into "Schizotypal-prone" and "Non-Schizotypal prone" by dividing the total SPQ score into three groups (Schizotypal-prone N=84, Average Schizotypal N=76, Non-Schizotypal prone N=75). Following this, the Schizotypal-prone group was further categorized as "Negative Schizotypal" (N=21) or "Positive Schizotypal" (N=43) with a median split analysis. Demographic variables [subjects' age, years of education, IQ (Raven score), cigarettes smoked/day, parental age at birth] were compared between the two groups using either parametric or non-parametric analysis of variance as appropriate. Separate univariate ANOVAs of each cognitive factor score were conducted, using the Schizotypy group as the between-subjects' factor.

Part C’
Results

Principal component analysis of cognitive variables

A total of 36 variables were included in the analysis, and eleven factors were extracted. Namely, the factors were: 1) Perseveration (comprising WCST categories completed, unrelated cards, Milner-perseverative errors, Milner and Nelson non-perseverative errors; Eigenvalue: 5.742, variance explained: 18.52%); 2) Declarative memory (comprising WL correct responses in the immediate, short-delay and long-delay recall; Eigenvalue: 3.228, variance explained: 10.41%); 3) Problem Solving (comprising SOC problems solved with the minimum number of moves and mean moves; Eigenvalue: 2.393, variance explained 7.72%); 4) Inattention (comprising WL intrusion errors in the immediate, short-delay and long-delay recall; Eigenvalue: 1.939, variance explained: 6.25%), 5) Episodic Memory (comprising PAL total errors and total trials; Eigenvalue: 1.738, variance explained: 5.61%), 6) Cognitive Flexibility (comprising RTI 5-choice movement time, Stroop interference score, phonemic and semantic fluency number of switches, Eigenvalue: 1.678, variance explained: 5.41%), 7) Emotional decision making (comprising IGT total money won and total cards selected from the advantageous decks, Eigenvalue: 1.476, variance explained:4.76%), 8) Strategy Formation (comprising SWM between errors and strategy score; Eigenvalue: 1.389, variance explained: 4.48%), 9) Working Memory (comprising RVIP total correct responses and N-back total correct responses and total false alarms; Eigenvalue: 1.172, variance explained: 3.78%), 10) Cognitive Stability (comprising RVIP total false alarms and phonemic fluency perseverative errors and number of clusters; Eigenvalue: 1.123, variance explained: 3.62%) and 11) Planning (comprising SOC mean initial and mean subsequent thinking times; Eigenvalue: 1.044, variance explained: 3.37%). For this model, the KMO=0.674, $p<0.001$ and the total variance explained was 73.938% (Table 3).

Table 3.Principal components analysis factor loadings.

		1. Perseveration	2. Declarative memory	3. Problem Solving	4. Inattention	5. Episodic memory	6. Cognitive Flexibility	7. Emotional decision making	8. Strategy formation	9. Working memory	10. Cognitive stability	11. Planning
WCST	Categories completed	-0.910										
	Unrelated cards	0,729										
	Milner pe	0,734										
	Nelson pe	Factor solution <0.5; variable excluded from analysis										
	Milner npe	0,842										
	Nelson npe	0,919										
WL	Correct immediate		0,652									
	Correct short-delay		0,846									

		1. Perseveration	2. Declarative memory	3. Problem Solving	4. Inattention	5. Episodic memory	6. Cognitive Flexibility	7. Emotional decision making	8. Strategy formation	9. Working memory	10. Cognitive stability	11. Planning
	Correct long-delay		0,864									
	Intrusions immediate				0,820							
	Intrusions short-delay				0,816							
	Intrusions long-delay				0,745							
SOC	Problems			-0,907								
	Mean move			0,890								
	Mean ITT											0,837
	Mean STT											0,616
PAL	Errors					0,868						

		1. Perseveration	2. Declarative memory	3. Problem Solving	4. Inattention	5. Episodic memory	6. Cognitive Flexibility	7. Emotional decision making	8. Strategy formation	9. Working memory	10. Cognitive stability	11. Planning
	Trials					0,851						
RTI	5-choice movement						-0.462					
	5-choice reaction	Factor solution <0.5; variable excluded from analysis										
SWM	Between err								0.840			
	Within err	Factor solution <0.5; variable excluded from analysis										
	Strategy								0.868			
RVIP	Total correct									-0.474		
	Total FAR										0.689	
Stroop	Interference						0.496					
VF	Phon						0.742					

		1. Perseveration	2. Declarative memory	3. Problem Solving	4. Inattention	5. Episodic memory	6. Cognitive Flexibility	7. Emotional decision making	8. Strategy formation	9. Working memory	10. Cognitive stability	11. Planning
	switche											
	Phon cluster										0.560	
	Phon pers										0.751	
	Sem switche						0.754					
	Sem cluster	Factor solution <0.5; variable excluded from analysis										
	Sem pers	Factor solution <0.5; variable excluded from analysis										
IGT	Money won							0.919				
	Adv cards							0.913				
N-back	Total correct									-0.559		
	Total FAR									0.787		

WCST-Wisconsin Card Sorting Task, Milner pe-Milner Perseverative Errors, Milner npe-Milner non perseverative errors, Nelson pe-Nelson Perseverative errors, Nelson npe-Nelson non perseverative errors, WL-Word Lists, SOC-Stockings of Cambridge, Mean ITT-Mean Initial Thinking Time, Mean STI-Mean Subsequent Thinking Time, PAL-Paired Associates Learning, RTI-Reaction Time, SWM-Spatial Working Memory, Between err-Between Errors, Within err-Within Errors, RVIP-Rapid Visual Information Processing, Total FAR-Total False Alarms, VF-Verbal Fluency, Phon Switche-Phonemic Switches, Phon Cluster-Phonemic Clusters, Phon Pers-Phonemic Perseverations, Sem Switche-Semantic Switches, Sem Cluster-Sematic Cluster, Sem Pers-Semantic Perseverations, IGT-Iowa Gambling Task, Adv Cards-Advantageous Card

Association of cognitive factors with Schizotypy scores

Pearson correlations between the PCA cognitive factors, demographic variables and SPQ scores revealed significant correlations only between the cognitive factors and age as well as number of cigarettes smoked/day (all p values <0.05).

When Positive Schizotypy score entered the independent variable list, we obtained significant models in the case of "Perseveration" [$F(3,234)=5.73$, $p<0.001$; R: 7.3 (adjusted R^2: 6.1)], "Declarative Memory" [$F(3,220)=5.73$, $p<0.001$; R: 3.0 (adjusted R^2: 1.7)] and "Episodic Memory [$F(3,220)=2.75$, $p<0.05$; R: 3.5 (adjusted R^2: 2.2)]. The model was not significant for the remaining factors (all p values >0.1). Backward regressions revealed that (a) 7.1% (Adjusted R^2: 6.7%) of the "Perseveration" variance was significantly predicted by high positive Schizotypy (Beta= 0.27; t= 4.10, $p<0.001$), (b) 2.6% (Adjusted R^2: 2.2) of the "Declarative Memory" variance was significantly predicted by low positive Schizotypy [Beta= -0.16, t= -2.51, $p<0.02$] and c) 2.7% (Adjusted R^2: 2.3) of the "Episodic Memory" variance was significantly predicted by high positive Schizotypy [Beta= 0.17, t= 2.52, $p<0.02$].

When Negative Schizotypy score entered the independent variable list, we obtained significant models in the case of "Declarative Memory" [$F(3,234)=3.07$, $p<0.03$; R: 3.8 (adjusted R^2: 2.6)] The model was not significant for the remaining factors (all p values >0.1). Backward regressions revealed that (a) 3.6% (Adjusted R^2: 3.2%) of the "Declarative Memory" variance was significantly predicted by low negative Schizotypy (Beta= -0.19; t= -2.92, $p<0.005$).

When the total Schizotypy score entered the independent variable list, we obtained significant models in the case of "Perseveration" [$F(3,234)=3.44$, $p<0.02$; R: 4.5 (adjusted R^2: 3.2)], "Declarative Memory" [$F(3,220)=2.64$, $p<0.005$; R: 3.3 (adjusted R^2: 2.1)] and "Episodic Memory [$F(3,220)=2.96$, $p<0.05$; R: 3.8 (adjusted R^2: 2.5)]. The model was not significant for the remaining factors (all p values >0.1). Backward regressions revealed that (a) 4.2% (Adjusted R^2: 3.7%) of the "Perseveration"

variance was significantly predicted by high total Schizotypy (Beta= 0.20; t= 3.08, $p<0.002$), (b) 3.1% (Adjusted R^2: 2.6) of the "Declarative Memory" variance was significantly predicted by low total Schizotypy [Beta= -0.18, t= -2.71, $p<0.01$] and c) 2.8% (Adjusted R^2: 2.4) of the "Episodic Memory" (i.e. more errors and more trials to complete the task) variance was significantly predicted by high total Schizotypy [Beta= 0.17, t= 2.57, $p<0.02$].

Categorical analyses

Descriptives and demographics

The mean (±SD) of the SPQ sub-scale scores and the demographic variables of the three groups are presented in **Error! Reference source not found.**. The three groups differed significantly in age and years of education and tended to differ significantly in the number of cigarettes smoked daily. They also differed significantly in the Disorganization subscale of the SPQ, in the TCI Harm avoidance and Self-Transcendence as well as in the SCL Depression and Anxiety subscales. Therefore these variables were taken as covariates in the categorical analyses that follow.

Table 4.SPQ scores and demographic variables mean (±SD) of the groups

	Non-Schizotypal prone (n=75)	Positive Schizotypal (n=43)	Negative Schizotypal (n=21)	P value
Positive Schizotypy	5.29±2.95	20.51±3.31	13.29±3.52	<0.001
Negative Schizotypy	2.31±1.95	12.65±5.64	17.10±5.20	<0.001
Disorganised Schizotypy	1.48±1.71	8.00±3.29	8.48±3.82	<0.001
Age	21.35±2.68	20.95±2.35	19.57±1.54	<0.02
Years of education	13.71±2.02	13.16±1.45	12.33±0.97	<0.005
Cigarettes smoked/day	5.13±8.21	4.79±6.76	0.86±2.43	>0.05
Raven raw score	48.47±6.82	45.88±9.33	46.52±12.12	>0.2
Paternal age at birth	31.30±5.50	30.79±6.34	32.17±7.25	>0.5
Maternal age at birth	25.27±7.44	25.81±5.49	26.56±5.11	>0.7
TCI Harm Avoidance	5.91±4.07	8.16±3.88	9.48±3.52	<0.001
TCI Self-Transcendence	8.08±2.91	9.23±3.00	7.00±3.00	<0.001
SCL Depression	0.40±0.39	1.04±0.72	1.36±0.73	<0.001
SCL Anxiety	0.21±0.27	0.77±0.66	0.90±0.56	<0.001

Categorical analyses for the cognitive data

We found significant group effects for the PCA factors "Perseveration" [$F(2,125)=4.69$, $p<0.02$; $\eta^2=.075$], "Problem Solving" [$F(2,125)=3.19$, $p<0.05$; $\eta^2=.053$] and "Inattention" [$F(2,125)=3.31$, $p<0.05$; $\eta^2=.055$] (all p values for the remaining PCA factors >0.1). Bonferroni post hoc tests showed that the Non-Schizotypal prone group had lower Perseveration (i.e. fewer perseverative errors and more completed categories in the WCST, $p<0.02$) and higher Problem Solving ($p<0.05$) compared to the Positive Schizotypal group. The negative Schizotypal group had lower Inattention compared to the Positive Schizotypal group ($p<0.05$) (Figure 10).

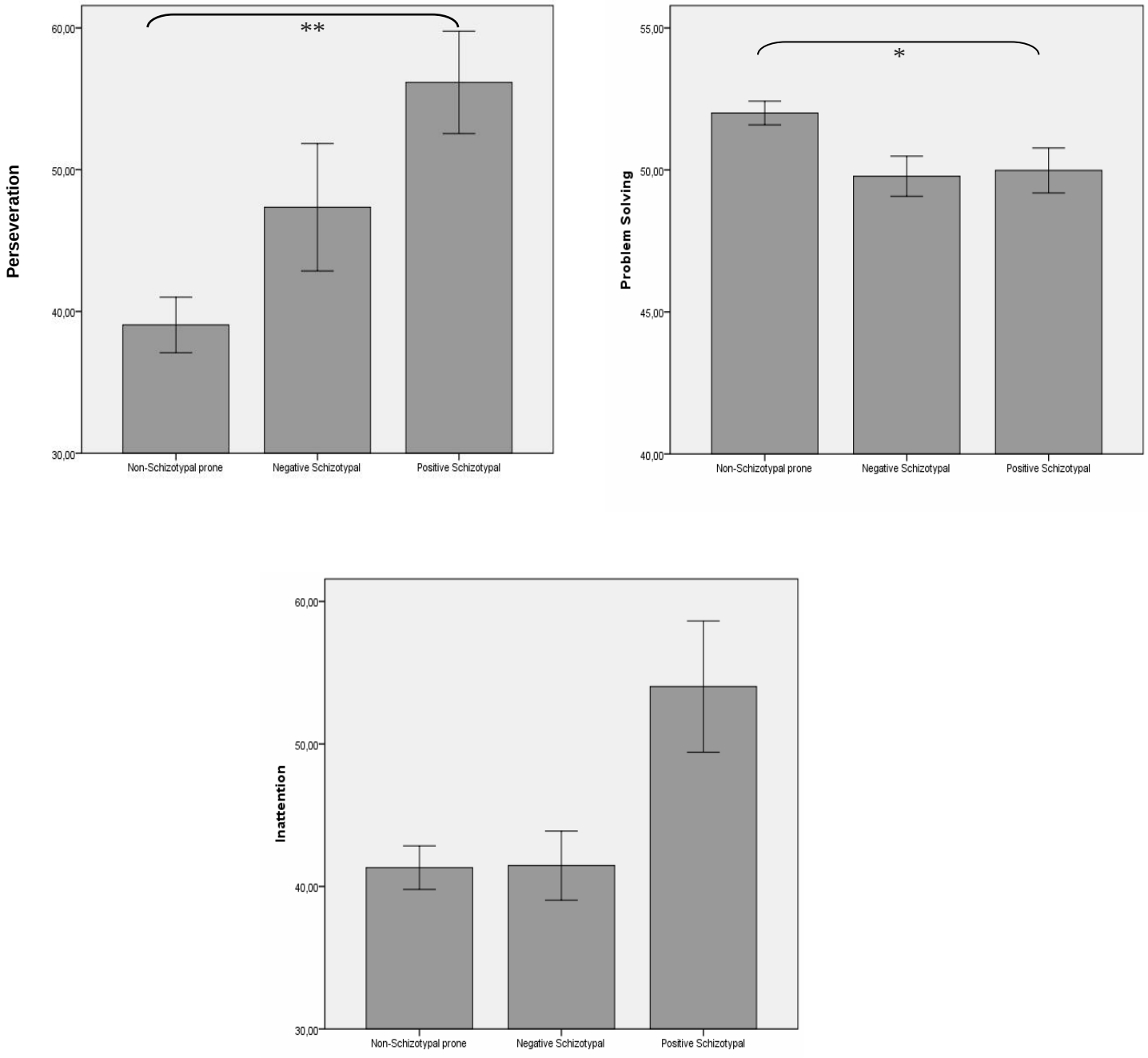

Figure 10 PCA factors for the three groups.

Z scores were transformed to T-scores for the graphical representation[1]. Columns represent group means and bars represent SEM. **p<0.02; *p<0.05.

[1] Z-scores can be transformed into t-scores by multiplying each score by 10 and then adding 50. The transformation is suggested for graphic purposes, as t-scores are always positive and therefore easier to understand (Grillon et al, 2003).

Analyses of the startle data

Of the 139 subjects, 47 were startle non-responders leaving 47 subjects in the Non-Schizotypal prone group, 33 subjects in the Positive Schizotypal group and 12 subjects in the Negative Schizotypal group. After the application of standard exclusion criteria, another two subjects from the Negative Schizotypal group were excluded. Therefore the analyses were conducted only between the Non-Schizotypal and the Positive Schizotypal group. Identical regression and categorical analyses as with the cognitive data were performed. No significant differences were found in any analysis (al p values >0.1).

Part D'
Discussion

The primary aim of the study was to elucidate the effects of positive and negative schizotypal traits on cognitive functions and PPI in the general population. We found that positive schizotypy predicted a quite significant art of the variance in the "Perseveration" index; this was further confirmed by the categorical analyses, according to which participants with high levels of positive schizotypy also scored higher in "Perseveration" (i.e. they completed fewer categories, made more perseverative and non-perseverative errors in the WCST). Similarly to our results, positive schizotypy has been associated with poorer performance on the WCST and more perseverative errors (Poreh et al, 1995; Suhr et al, 1997; Gooding et al, 2001; Lenzenweger et al, 1994), further supporting the existence of a widely distributed neural network including both cortical and subcortical brain structures (Fernandez-Duque et al, 2001; Posner et al, 1990) that mediated performance in the WCST (Nyhus et al, 2009).

We also found that both positive and negative schizotypy predict "Declarative Memory". High positive schizotypy also predicted part of the variance of the "Episodic memory" factor and total schizotypy score also predicted declarative and episodic memory. These findings are in accordance with and further expand the study by Bo-Yeon Song et al, (2011), who showed that individuals with schizotypal traits (high SPQ total score, including both positive and negative scores) have impaired declarative memory.

In the categorical analysis, we found that only the Positive Schizotypy group scored lower in the PCA factor "Problem solving", compared with the Non-Schizotypal prone group. An interesting theory (Weinberger et al, 1986) proposes a dopaminergic imbalance in schizophrenia, which this determines the positive and negative symptoms of the disease: the dorsolateral prefrontal cortex and its connections, due to hypo-active stimulation of the DR_1 receptors lead to prefrontal dopaminergic hypo-activity and this, in turn, leads to the clinical presentation of the negative symptoms.

Dopaminergic hypo-activity in the mesocortical pathway was hypothesized to lead to disinhibition and overactivity of the mesolimbic dopamine pathway (hyper-stimulation of DR_2 receptors), resulting in positive symptoms. Differences in dopaminergic activity are correlated with positive and negative schizotypy (Siever et al, 1995). "Hyper-dopaminergia" in subcortical mesolimbic structures may lead to positive symptomatology, such as ideas of reference, unusual perceptual experiences, magical ideation and "Hypo-dopaminergia" in the prefrontal cortex is associated with negative symptomatology such as apathy, avolition, asociality, affective flattening. Schizotypal subjects with predominantly negative symptom presentation may be more likely to display executive function and working memory deficits (Din et al, 2002), while individuals with positive symptoms may display memory and attention deficits (Suhr et al, 2001). However, Vollema et al, (2002) who also investigated the neurocognitive correlates of positive or negative schizotypy in unaffected first degree relatives of schizophrenia patients, found that Positive Schizotypy was "slightly" correlated to verbal long-term memory (a Temporal-Limbic Task), while Negative Schizotypy was not correlated to any prefrontal measure (e.g. WCST, Verbal Fluency Test). Therefore, although the findings are limited, the hypothesis that prefrontal malfunctioning underlies negative schizotypy requires further investigation. Also, the study by Vollema et al, (2002) and the present results raise questions about the exact neural correlates of the separate dimensions of schizotypy. There is evidence by neuroimaging studies (see Introduction) indicating that positive schizotypy is not limited to subcortical abnormalities, as high positive schizotypal subjects also present with reduced activation in the left dorsolateral prefrontal cortex (Mohanty et al, 2005), reduced grey matter volume in Medial PFC and Orbital PFC (Ettinger et al, 2011), and reduced white matter integrity in frontotemporal white matter tracts (Nelson et al, 2011).

Another hypothesis for the interpretation of our result is that the dichotomous version of the SPQ that was employed in the present study does not fully discriminate between the positive and negative schizotypal traits. Wuthrich et al, (2005) developed a Likert version of the SPQ and found that a high percentage of the population is more willing to disclose schizotypal symptoms using a Likert than a forced choice format. Moreover, Cohen et al, (2010), also used a Likert version of the scale and found greater sensitivity compared with the dichotomous version.

Finally, we found that the Negative Schizotypal group had lower "Inattention" (i.e. less intrusion errors in the immediate, short- and long-delay recall of the Word Lists task) compared with the Positive Schizotypal group. In accordance to this, positive schizotypy has been found to be more associated with attention impairments (Bergida et al, 2006; Gooding et al, 2006; Granger et al, 2012).

No significant effects of schizotypy were found in any PPI or startle measure. One major limitation of the study is the small sample size of the schizotypal groups, which became even smaller when excluding the startle non-responders. Stefanis et al, (2006) studied 1355 healthy males and suggested that the cut-off score of identifying Schizotypal subjects is a total score of 44/74 in the SPQ. However, in our sample only few subjects fulfilled this criterion. Thus, we can hypothesize that PPI deficits may be associated with more extreme scores on the dimensions of schizotypy and that the small number of the participants probably did not give us the power required to detect all possible associations between positive or negative schizotypy and PPI.

A second limitation of the study was the inclusion only of male subjects, thus reducing the generalisability of the findings. Third, as regards the cognitive findings, it is well established that most tasks tap more than one cognitive functions. For example, the WCST assesses mainly executive function processes but performance also depends on working memory capacity (Strauss et al, 2006). Consequently, it is difficult to match a cognitive function with the function of one specific brain area and a specific type of symptomatology.

To sum up, we have found that positive and negative schizotypy is associated with some aspects of cognitive function but not PPI, partially confirming our initial hypothesis. The present findings, however, are preliminary and further cognitive, neuroimaging and genetic studies are required, in order to further elucidate the distinct profile of positive and negative schizotypy.

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Abbreviations

ADHD	Attention deficit hyperactivity disorder
ANOVAs	Analyses of variance
CANTAB	Cambridge neuropsychological test automated batteries
COMT	Catechol-O-methyltransferase
COWAT	Controlled Oral Word Association Test
CPT	Continuous performance task
CRN	Cochlear root nucleus
CSF	Cerebrospinal fluid
DA	Dopamine
DCN	Dorsal cochlear nucleus
DR_1	Dopamine receptor 1
DR_2	Dopamine receptor 2
DTI	Diffusion tensor imaging
EMG	Electromyography
EPQ	Eysenck psychotism scale
FA	Fractional anisotropy
fMRI	Functional magnetic resonance imaging
GMD	Grey matter density
GSI	Global severity index of SCL-90
IC	Inferior colliculi
IGT	Iowa gambling task
ITT	Initial thinking time Stockings of Cambridge
MMPI	Minnesota multiphasic personality inventory
O-LIFE	Oxford-Liverpool inventory of feelings & experiences
PAL	Paired associates learning
PAS	Perceptual aberration scale
PET	Positron emission tomography
PCA	Principal Component Analysis
PerAb	Perceptual aberrations
PFC	Prefrontal cortex

PhysAn	Physical anhedonia
PNC	Caudal pontine reticular nucleus
PPI	Prepulse inhibition of the acoustic startle response
PSDI	Positive symptom distress index of SCL-90
PST	Positive symptom total of SCL-90
RTI	Reaction Time
RVIP	Rapid visual information processing
SART	Sustained attention response to task
SC	Superior colliculi
SD	Standard deviation
SCL-90	Symptom Checklist 90
SIT	Stroop interference test
SOAs	Stimulus onset asynchronies
SOC	Stockings of Cambridge
SPD	Schizotypal personality disorder
SPECT	Photon emission computed tomography
SPL	Sound pressure levels
SPQ	Schizotypal personality questionnaire
STA	Schizotypy traits questionnaire
STT	Subsequent thinking time Stockings of Cambridge
SWM	Spatial working memory
TCI	Cloninger's temperament and character inventory
VBM	Voxel based morphometry
VCN	Ventral cochlear nucleus
VF	Verbal fluency
VmPFC	Ventromedial prefrontal cortex
WCST	Wisconsin card sorting test
WL	Word Lists