FACULTY OF PSYCHOLOGY AND EDUCATIONAL SCIENCES

EXPLORING THE RELATIONSHIP BETWEEN NORADRENALINE AND SCHIZOTYPAL TRAITS

A STUDY OF NOVEL AND CONSCIOUS INFORMATION PROCESSING

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Corona Verklaring Vooraf

Gezien de datacollectie nog niet was afgerond bij ingaan van de maatregelen tegen de verspreiding van het coronavirus is er besloten om te werken met een kleinere sample size. Gegeven 10% reductie in sample size was het nog mogelijk de analyses op een correcte manier uit te voeren, mits het selecteren van een analysetechniek waarbij de data niet werd geaggregeerd.

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Abstract

Schizotypy is a latent personality organization, thought to represent a vulnerability for schizophrenia spectrum disorders. Multiple similarities with schizophrenia have been reported; in terms of neurobiology, perception, cognitive and motor functioning deficits, amongst others. The psychosis risk signified by schizotypy can be regarded as a continuum, given that schizotypal traits and symptoms occur in the general population. Accordingly, studying underlying mechanisms in a subclinical sample can improve our understanding on how they could cause, perpetuate or contribute to schizophrenic symptomatology. One such potential causal factor, primarily related to disturbed cognitions (e.g. disorganised thinking, memory deficits, difficulty expressing thoughts), is a dysfunction in the noradrenergic system, which might affect conscious access to information. However, there is little to no research that directly investigates this proposed mechanism in a healthy at-risk population. Hence, to test the role of the locus coeruleus noradrenergic system in the different stages of conscious and novel information processing, 54 healthy volunteers (aged 16-35) with schizotypy scores ranging from minimal to subclinical levels performed a four-condition auditory oddball task. Throughout the task, their pupillary responses were recorded. While no significant effect of cognitive disorganised schizotypy on pupil dilation was found, surprisingly, a positive association between the cognitive disorganised schizotypy factor and performance in perception of sensory differences at an individualised threshold could be observed. Our results underscore the continuous and complex nature of the multidimensional construct that is schizotypy.

Nederlandstalige samenvatting

Schizotypie is een latente persoonlijkheidsstructuur die geacht wordt een schizofrenie kwetsbaarheid voor te stellen. Verschillende overeenkomsten met schizofrenie werden gevonden: op vlak van neurobiologie, perceptie, cognitieve- en motorische problemen. Dit psychoserisico geassocieerd met schizotypy kan worden beschouwd als een continuüm, gezien schizotypische persoonlijkheidsfactoren en symptomen in de algemene populatie voorkomen. Bijgevolg kan het onderzoeken van onderliggende mechanismen in een subklinische populatie ons begrip verbeteren van hoe deze factoren schizofrene symptomatologie kunnen veroorzaken, er toe bijdragen of instandhouden. Eén zulke potentiële causale factor, voornamelijk gerelateerd aan verstoorde cognities (bvb. gedesorganiseerd denken, geheugenproblemen, moeilijkheden met gedachten uit te drukken), is een dysfunctioneren van het noradrenerge systeem, wat de toegang tot bewuste informatie zou kunnen aantasten. Echter, er is weinig tot geen onderzoek die dit verondersteld mechanisme rechtstreeks bestudeert in een gezonde risicopopulatie. Bijgevolg, om de rol van het locus coeruleus noradedrenerge system te testen in de verschillende fasen van bewuste en nieuwe informatieverwerking, voerden 54 gezonde vrijwilligers (leeftijd 16-35) met schizotypie scores variërende van minimaal tot subklinisch, een auditieve oddball taak met vier condities uit. Doorheen de taak werden hun pupilresponsen gemeten. Terwijl er geen duidelijk significant effect van schizotypie op de pupildilataties werd gevonden, was er een positieve associatie tussen de cognitief gedesorganiseerde schizotypie factor en de prestatie op trials waarin sensoriële verschillen op de individuele waarnemingsgrens werden bevraagd. Onze resultaten benadrukken dat schizotypie een complex en multidimensionaal construct is, gelegen op een continuüm.

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Introduction

Schizotypy

Schizotypy is often described as a latent personality organisation that manifests itself as a set of personality characteristics related to the vulnerability to schizophrenia spectrum disorders (Rosell et al., 2015). More precisely, it is considered to be a multidimensional construct that can be observed in personality features, subclinical traits and clinical behaviour (Kwapil & Barrantes-Vidal, 2014). Individuals with elevated schizotypy show subtle but widespread changes in perception, cognitive or motor functioning.

History

Schizotypal traits were first described in the early twentieth century, when Bleuler (1924) used the term schizoid personality to describe patients and their relatives with no evident psychotic symptoms but schizophrenic traits such as social anxiety and disordered thinking. Furthermore, Kraepelin (1919) mentioned schizotypal symptoms as the precursor to dementia praecox, later referred to as schizophrenia. However, Rado (1953) was the first author to use the term schizotypy, as a shortened designation for the schizophrenic phenotype, a schizotypic personality organisation, which he attempted to link to genetic factors of schizophrenia. According to Rado (1953), schizotypal overt behaviour arises from a genetic vulnerability to schizophrenia. Its underlying schizotypal traits are present during the whole lifespan of patients, allowing for fluctuations in symptoms from mild impairments to open psychotic episodes.

Quasi-dimensional view

Along this line of advancements and building further on the work of Rado, Meehl (1962) developed a model describing the cause and biological mechanisms of schizophrenia-like conditions, proposing that a single schizogene underlies the predisposition to develop schizotypy and schizophrenia spectrum disorders. Within this quasi-dimensional view, schizotypy is regarded as set of personality traits observable in the behaviour and psychological characteristics of a small part of the general population. While Meehl (1990) presumed schizotypy does not necessarily result in a diagnosis of schizophrenic-like illness, he did assume that the joint occurrence of the schizotypal vulnerability and other polygenetic ‘potentiators’ or environmental stressors, for example traumatic experiences, result in the onset of schizophrenia. This view gained substantial support from later work and is reflected

in the so called ‘two-hit’ hypothesis of schizophrenia (for a review: see Davis et al., 2016; Oliver et al., 2020).

As opposed to this taxonic view on schizotypy, another line of research, rooted in differential psychology, emerged in the late twentieth century. A substantial influence on these studies came from the work of Eysenck (1947), whose biological theory of personality and personality disorder stated that all personality dimensions are fully determined by genetics. This contradicts Meehls (1962) notion of the schizogene as a vulnerability that only leads to an overt manifestation under certain environmental circumstances. Eysenck (1992) hypothesized that all behaviour can be captured by three personality dimensions: introversion/extraversion, neuroticism/stability and psychoticism, the latter characterized by impulsivity, aggression, and a lack of empathy. At the phenotypic level, Eysenck (1992) suggested that the combination of a certain pattern of extraversion and neuroticism and extreme values on psychoticism results in psychotic disorders such as schizophrenia. Thus, according to the model, these clinical syndromes differ in a quantitative manner only from healthy personality displays.

Fully dimensional view

Building on these foundations of the continuum between healthy and disordered personality, Claridge and Beech (1995) developed an important dimensional model on schizotypy and schizotypal personality disorder. Their model originates from research on normal personality variations. It accentuates that schizotypy is a dimensional trait that can result both in clinical and adaptive manifestations in personality, perceptual experiences and cognitive styles, for example creativity. Claridge and Beech (1995) assumed that the variances in personality, genetic and environmental factors that cause schizotypy are normally distributed in the general population. This is in contradiction to Meehls (1962) work, who postulated that schizotypal personality traits are only present in about 10% of the general population. Thus, according to Claridge and colleagues (1997) there exists a benign form of schizotypy: i.e. proneness to psychosis does not necessarily imply illness, it is in fact ‘neutral to pathology’. Only the joint occurrence of genetic and environmental influences will cause pathology. In conclusion, the model of Claridge and Beech (1995) entails a fully dimensional model of schizotypy, as opposed to Meehls (1962) idea of a clear differentiation between health and illness.

Over the last years, evidence in favour of this fully dimensional view has accumulated. A significant amount of studies have reported schizotypal symptoms in the general population (e.g. Fonseca-Pedrero et al., 2018; Nelson, Seal, Pantelis & Philips, 2013). For example, a study from Noguchi and colleagues (2008) reported schizotypal symptoms in a large sample of healthy adults, where high schizotypy levels were associated with negative outcomes such as decreased verbal IQ. Thus, even on the non-clinical level, schizotypy affects cognitive functioning (Ettinger et al., 2015). This continuum of symptom severity and cognitive impairments with schizophrenia at the extreme, is in line with the fully dimensional view (Kwapil et al., 2017; Linscott & Van Os, 2013; Noguchi, Hori & Kunugi, 2008).

Likewise, on the neurological level, healthy individuals with schizotypal personality features show similarities with schizophrenia (Bollini et al., 2007; Kaczorowski, Barrantes-Vidal & Kwapil, 2009). For instance, in the study from Bollini et al. (2007), neurological soft signs, small impairments in motor functioning and sensory perception, commonly found in schizophrenia, were present in healthy adults with schizotypal characteristics. Brain imaging studies consistently show partial structural and functional overlap between schizotypal and schizophrenic individuals (Acosta, Strauber & Kirchner, 2018; Ettinger et al., 2012; Meller, Ettinger, Grant & Nenadić, 2019; Soliman et al., 2008).

Overall, research indicates that schizotypal personality features and associated cognitive and neuropsychological disruptions are not confined to a small subset of the general population. Consequently, in this dissertation, the fully dimensional view is employed.

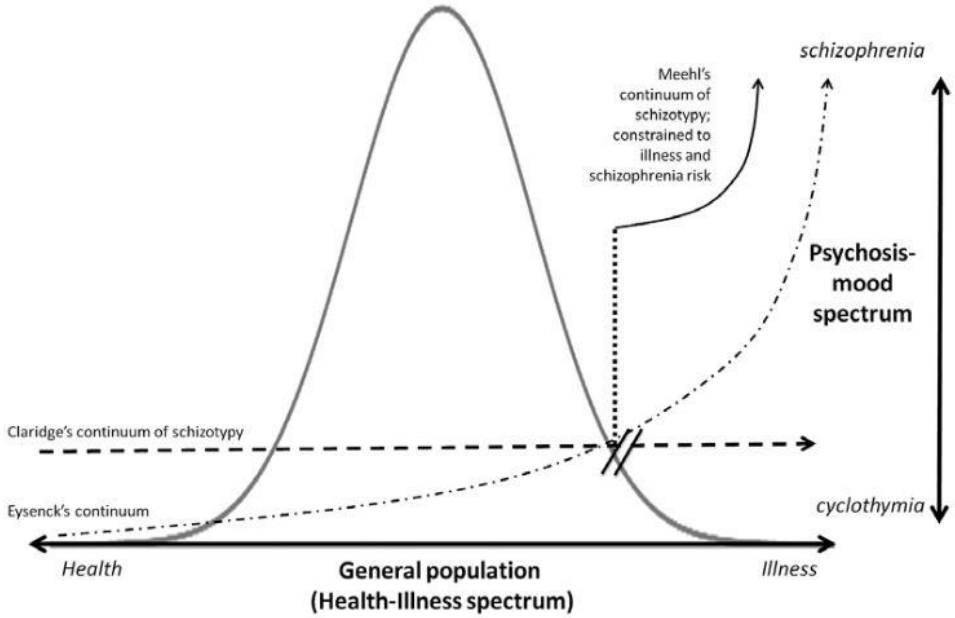

Figure 1: Models of schizotypy (Grant, Green & Mason,2018)

In conclusion, schizotypy is a heterogenous construct with multiple possible underlying causes, manifestations, and outcomes (Kwapil & Barrantes-Vidal, 2014). This heterogeneity is also reflected in the variety of measures of schizotypy: a large amount of screening questionnaires based on both taxonic and fully dimensional perspectives have been established over the years. Based on Meehl's work, self-report scales on perceptual body-image aberration (Chapman, 1978), physical and social anhedonia (Chapman, 1978; Eckblad et al, 1982) and magical ideation (Eckblad & Chapman, 1983) were developed. Furthermore, rooted in psychopathology literature and based on the DSM III-R criteria for schizotypal personality disorder, Raine (1991) assembled the Schizotypal Personality Questionnaire (SPQ). The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) (Mason, Claridge & Jackson, 1995) on the other hand, is a four-factor scale to assess schizotypy in non-clinical individuals, based on the full dimensional perspective of Claridge and Beech (1995). It discriminates three dimensions of schizotypy: *cognitive disorganisation*, *introvertive anhedonia* and *unusual experiences* and evaluates borderline and antisocial traits with a fourth factor, *impulsive nonconformity*. The cognitive disorganised factor encompasses difficulties with (working) memory, concentration, attention, decision-making and is related to perceptual information processing deficits and social anxiety. Whereas *cognitive disorganisation* is linked to the fear for social interaction, *introvertive anhedonia* refers to a lack of enjoyment from social interaction and intimacy, as well as decreased

enjoyment in general. Lastly, the *unusual experiences* factor is associated with perceptual aberrations such as hallucinations, in addition to unusual and magical thinking, related to delusions in schizophrenia (Ettinger et al., 2015; Mason, Claridge & Jackson, 1995).

Structure of schizotypal personality traits and their outcomes

Research using factor analysis on the structure of these traits measured with the aforementioned self-report questionnaires has consistently indicated the existence of a three-factor solution (Cohen et al., 2015, Vollema & van den Bosch, 1995). Interestingly, a recent study in the general population (n= 11807) explored the network structure of schizotypal traits as captured by the shortened version of the O-LIFE (Polner et al., 2019). Evidence was found for the separation of the 3 schizotypy factors (*cognitive disorganisation*, *introvertive anhedonia* and *unusual experiences*). Furthermore, the network model demonstrated that *cognitive disorganisation* is likely to be found in combination with both elevated *unusual experiences* and *introvertive anhedonia* scores, although the underlying mechanism of this finding remains to be investigated (Polner et al., 2019).

Others argue for a four factor solution to capture all schizotypal traits (Compton, Goulding, Bakeman & McClure-Tone, 2009), including *negative schizot*ypy (e.g. aloofness, reduced emotional expression), *positive schizotypy* (e.g. magical thinking, psychotic-like symptoms), *interpersonal sensitivity* (e.g. social anxiety, sensitivity), and *social isolation/introversion* (Linscott & Morton, 2017; Vollema & van den Bosch, 1995). This positive vs negative discrepancy resembles the two syndromes concept of schizophrenia, where the positive one is related to psychotic symptoms such as hallucinations and delusions, while the other syndrome is linked with restricted affect and anhedonia (Crow, 1980).

Although proponents of the fully dimensional view argue that schizotypal traits do not necessarily manifest themselves as pathological, there exists a large body of empirical evidence linking these traits to the incidence of a variety of adverse outcomes in terms of cognition, emotion and social functioning, amongst others.

In the general population, a recent longitudinal study showed that unaffected participants with elevated self-reported schizotypal traits faced a higher chance of suffering from mental health problems 3 years later. More specifically, positive

schizotypal symptoms at time point 1 predicted depressive symptoms, psychotic symptoms, lowered self-esteem and higher scores on schizophrenia-spectrum pathologies including avoidant, schizotypal and paranoid personality disorder questionnaires. Negative schizotypy traits predicted reduced social and occupational functioning, emotional disturbances and indications of schizotypal and schizoid personality symptoms (Racioppi et al., 2018). Moreover, cross-sectional studies demonstrated associations between self-reported schizotypy, anxious and depressive symptoms (Lewandowski et al., 2006; Campellone, Elis, Mote, Sanchez & Kring, 2016).

Additionally, in clinical populations at high risk for psychotic disorders, schizotypy measures can be useful to predict the individual risk of converting to psychosis (e.g. Flückiger et al., 2016). Indeed, there is an increase in schizotypal traits in non-psychotic first-degree relatives of schizophrenia spectrum disorders patients (Appels, Sitskoorn, Vollema & Kahn, 2004; Kendler, McQuire, Gruenberg, 1995; Linscott & Morton, 2017). The interpretation that schizotypy might be a risk factor for developing schizophrenia implies that schizotypal traits could be part of a prodromal phase (Barrantes-Vidal et al., 2013). In a seminal study by Lenzenweger and Loranger (1989), for example, first-degree relatives of non-psychotic psychiatric patients, mostly hospitalized, were examined. Patients were screened for personality disorders based on DSM-III-R criteria and crucially, relatives of schizotypal patients had been treated more often for schizophrenia than relatives of non-schizotypal patients. More recent work (Mata et al., 2003), where 263 relatives of people with psychosis completed measures of schizotypy, a cluster of symptoms reported by the patients (delusions, hallucinations and thought disturbance) was positively correlated with outcomes from all three measures of schizotypy used in their unaffected relatives. Furthermore, an older longitudinal study spanning fifteen years found that self-reported psychotic symptoms in children predict an increased risk of a schizophreniform disorder in adulthood (Poulton, Caspi, Moffitt, Cannon, Murray & Harrington, 2000).

Not only does schizotypy seems to predict the onset of psychiatric symptoms, it might also be an aggravating factor in the treatment of comorbid psychiatric conditions. For example, in obsessive-compulsive disorder (OCD) patients, where schizotypy is common (Sobin et al., 2000), studies suggest that schizotypal

personality characteristics are associated with the failure of cognitive-behavioural therapy for OCD (Moritz et al., 2004).

In addition to this clear relationship with psychological and emotional problems, there exists a strong connection between schizotypal personality features and cognitive dysfunctions (Ettinger et al., 2015). Meta-analyses show decreased functioning of verbal and visual-spatial working memory, language and performance on tasks that require cognitive control (Siddi, Petretto & Preti 2017; Steffens, Meyhöfer, Fassbender, Ettinger, & Kambeitz, 2018). For example, the latter meta-analysis on various aspects of cognitive control in non-clinical schizotypal populations revealed significant impairments in all but inhibitory executive functions (Steffens et al., 2018). Unsurprisingly, of all three factors the cognitive disorganised dimension seems to have a unique and large association with attentional deficits (Kemp, Bathery, Barrantes-Vidal & Kwapil, 2020). Moreover, researchers have urged to further investigate the cognitive disturbances in schizotypy in regard to the development of full-blown psychotic disorders (Demjaha, Valmaggia, Stahl, Byrne & McGuire, 2012; Flückiger et al., 2019). Indeed, Flückiger and colleagues (2019) emphasized the facilitating role of cognitive deficits in the conversion from schizotypal traits to clinical psychotic symptoms.

Hence, there is a wealth of findings that support the notion of schizotypy as psychosis proneness. This risk can be situated on a continuum, assuming that subclinical schizotypic traits and symptoms occur in the general population. For this reason, schizotypal samples are a useful group to study the aetiology of schizophrenia spectrum and psychotic disorders (Ettinger et al., 2014; Lenzenweger, 2006; Nelson et al., 2013). Apart from this, there is a need to study schizotypy itself since it is intrinsically correlated with maladaptive outcomes, neurocognitive impairments and social and emotional problems.

Noradrenaline and the schizophrenic spectrum

Traditionally, the majority of research on the biochemical basis of schizophrenia has focused on the role of dopamine and to a lesser extent on glutamate. The notion that disruptions in the dopaminergic system has a causal role in the development of psychotic illnesses can be traced back to the late fifties (Connell, 1957*).* An important impellent for the dopamine hypothesis was the discovery that chlorpromazine is effective in treating psychosis due to its potency to block dopamine D2 receptors (Winkelmans, 1954; York, 1972). Subsequently, new generations of antipsychotic drugs have mainly targeted dopamine receptors, often in combination with serotonin and noradrenergic modulation (e.g. Miyamoto et al., 2012). Still, their efficacy remains very limited for negative and cognitive disorganised symptoms (Galderisi, Mucci, Buchanan & Arango, 2018; Miyamoto et al., 2012). Indeed, the blunted affect, amotivation and disordered thinking symptoms do not fit well in the 'aberrant salience hypothesis': i.e. that a hyperdopaminergic state causes patients to place inappropriate significance on neutral stimuli (e.g. visual or auditory), ultimately leading to psychosis (Kapur, 2003; Galderisi et al., 2018). Hence, it is plausible that other neurotransmitter or immune-related processes are of importance in the aetiology of schizophrenia, and by extent schizotypy, given their resemblances on the genetic and neurobiological level (De Picker, Morrens, Chance & Boche, 2017; Ettinger et al., 2014). Indeed, also in schizotypy, the involvement of striatal dopamine has been demonstrated (Howes et al., 2011; Soliman et al., 2008) and some studies support the aberrant saliency hypothesis in positive schizotypy (Chun, Kwapil & Brugger, 2019). Interestingly, one fMRI study found that participants with negative schizotypy in a hyperdopaminergic state (by means of administering L-DOPA), compared to placebo, showed similar decoupling patterns between striatal and occipitotemporal regions, supporting the aberrant saliency hypothesis (McCutcheon, Abi-Dargham & Howes, 2019), as found in positive schizotypy individuals, independent of the drug/placebo condition (Rössler et al., 2018). Again, as in schizophrenia, the dopamine hypothesis seems only explanatory for a subset of symptoms or characteristics (Chun, Kwapil & Brugger, 2019; Wang, Ettinger, Meindl & Chan, 2018). A noteworthy but understudied option in the search for additional neurobiological underpinnings of schizophrenia, is noradrenaline. While the role of dopamine remains undisputed, at least in a subset of symptoms, past research has argued for the role of the noradrenergic system and an integrative perspective on the two systems (Van Kammen & Kelley, 1991).

Noradrenaline, also referred to as norepinephrine, is a monoamine neurotransmitter mainly synthesized in a small nucleus in the brainstem known as the locus coeruleus (LC) (Berridge & Waterhouse, 2003). Its main functions are regulating the level of wakefulness and arousal, but LC neurons also seem responsive to novel, salient, emotional and unexpected stimuli or events (Berridge & Waterhouse, 2003; Aston-Jones & Cohen, 2005). The noradrenergic system is characterized by an extensive projection pattern across almost the whole cortex and is involved in attentional and sensory processes, stress responses and memory encoding (Aston-Jones & Cohen, 2005, Sara, 2015). For instance, the adaptive gain theory poses that the locus coeruleus noradrenergic system is responsible for the behavioural trade-off between exploring, searching for new behaviour, and exploiting, sustaining attention to a current task or behaviour (Aston-Jones & Cohen, 2005; Gilzenrat, Nieuwenhuis, Jepma & Cohen, 2010). Interestingly, although dopaminergic and the noradrenergic systems interact in the prefrontal cortex (Xing et al., 2016), the regions that are not innervated by noradrenaline are the striatum, substantia nigra and the globus pallidus, vital areas for the dopaminergic system. This implies a division in function of the two neurotransmitter systems, which in turn strengthens the hypothesis that they could play a complementary role in schizophrenia (Schwarz & Luo 2015; Swanson, 1976).

Originally hypothesized by Stein and Wise (1971), the view that increased noradrenergic neural signalling might play a causal role in the development of schizophrenia and especially its cognitive symptoms received a substantial amount of evidence (e.g. Steinhauer & Hakerem, 1992). The earliest indications for a dysregulation in noradrenaline originated from post-mortem studies, where increased noradrenaline levels in the patients' brains were found (Wise & Stein, 1975; Farley et al., 1978; Crow et al., 1979). Furthermore, this finding has been replicated in cerebrospinal fluid and blood plasma studies (Gomes, Shanley, Potgieter & Roux, 1980). It is often reported that patients with primarily positive symptoms, such as psychosis, had higher levels of CSF noradrenaline compared to patients with negative symptoms (Kemali, Maj, Galderisi, Ariano, & Starace, 1990). Furthermore, within these group of positive symptoms these findings seem especially true for cases of paranoid schizophrenia. This could be attributed to vigilance or arousal promoting function of noradrenaline. For instance, according to Hornykiewicz (1982), increased vigilance can cause paranoia. However, it appears as if there is not such a consistent correlation between elevated noradrenaline levels and the negative state of schizophrenia. An elegant hypothesis that might explain this discrepancy was

proposed by Yamamoto (2004). In this review, it was suggested that the origin of the two syndromes of schizophrenia could partially be caused by overactivity or underactivity of the central noradrenergic system. Overactivity is thought to be associated with positive symptoms (type I), while underactivity of the noradrenaline system corresponds with negative symptoms (type II).

Another line of evidence for the function of noradrenaline in schizophrenia and schizotypy is pharmacological research. As mentioned before, with the development of atypical antipsychotic drugs (e.g. olanzapine and quetiapine), that also act as α2-adrenergic receptor antagonists, it became clearer that not only dopamine but also noradrenaline contributes to the ontogenesis of psychosis and likely, schizotypal personality disorders (Fitzgerald, 2014; Seeman, 2004). Besides their effectiveness as antipsychotics, they seem to have beneficial effects on cognitive deficits in schizophrenia and alleviate side effects of concurrent typical antipsychotic treatment (Wadenberg, Wiker & Svensson, 2006; Woodward, Purdon, Meltzer & Zald, 2005; Uys, Shahid & Harvey, 2017). Moreover, some studies have shown that noradrenergic antidepressants such as serotonin and noradrenaline reuptake inhibitors (SNRIs) might be effective in relieving negative symptoms in schizophrenia (Terevnikov, Joffe & Stenberg, 2015, Uys et al., 2017). This can be interpreted as indirect evidence for a causal role of noradrenaline in schizophrenia spectrum disorders, as negative symptoms have been shown difficult to treat with classical antipsychotics, who do not target the noradrenergic system (e.g. Hanson, Healey, Wolf & Kohler, 2010). Finally, noradrenaline reuptake inhibitors (NRIs) could be effective as cognitive enhancers in schizophrenia (Maletic et al., 2017).

In conclusion, there are ample arguments in favour of an additional role of the noradrenergic system in mainly the cognitive and negative symptom clusters in schizophrenia. Nevertheless, there is virtually no research on possible noradrenaline dysregulation in schizotypy. Additionally, the exact mechanisms by which the noradrenergic system could possibly cause, perpetuate or alter schizophrenic symptomatology are unclear. Given that schizotypal traits likely precede the onset of schizophrenia, studying those mechanisms in schizotypal samples could benefit our understanding of the causal role of noradrenaline in schizophrenic spectrum disorders.

Impairments in conscious information processing

As reviewed, schizophrenia and schizotypy are accompanied with cognitive dysfunctions, which might be related to noradrenergic dysregulations. In a search for a unifying theory of the heterogeneous symptoms of the disorder, it has been proposed that disruptions of conscious processing might underlie the cognitive abnormalities in schizophrenia and possibly schizotypy (e.g. Frith, 1979; Sass & Parnas, 2003). For example, Yamamoto (2004) suggests that hypervigilant consciousness is related to positive symptoms, whilst a state of hypovigilance is associated with negative symptoms. As previously described, hypervigilance could lead to paranoia and delusions, whereas a hypovigilant and hyporesponsive state might cause cognitive impairment, anhedonia and overall blunted affect (Fitzgerald, 2014; Hornykiewicz,1982).

In order to meaningfully explore the role of impaired conscious information processing in schizotypy, it is desirable to clarify which operationalisation will be used. As such, according to the global neuronal workspace theory, consciousness can be defined as following: a non-transitive state in which a subject has 'access to conscious report' (Dehaene, Changeux, Naccache, Sackur & Sergent, 2006). Thus, if an individual is able to report the information, it was consciously processed. On the other hand, subliminal processing corresponds to information inaccessibility: stimuli are presented for a very short time or without sufficient intensity (Dehaene et al., 2006). Even though in this processing state the information is inaccessible to the subject, it might affect later task performance, which is defined as subliminal priming (Dehaene et al., 2006; Lohse & Overgaard, 2019). Besides these two extremes of conscious access, supposedly, there exists another so-called preconscious state of information processing; a transient state in which subjects are potentially able to access the information but have not yet done so (Dehaene, Changeux & Naccache, 2011). Studies on sensory information processing in schizophrenia patients consistently show decreased conscious processing. In visual backward masking experiments, in which a later stimulus blocks the conscious processing of an earlier, weaker or shorter stimulus, patients seem to have an elevated threshold for conscious perception (Charles et al., 2017; Favrod et al., 2018). As opposed to a reduced ability of consciously reporting and memorizing stimuli, remarkably, subliminal priming appears to be intact in schizophrenia (e.g. Del Cul et al., 2006).

These findings have been replicated in multiple studies employing both auditory and visual paradigms (Berkovitch, Dehaene & Gaillard, 2017; Caruana, Stein, Watson, Williams & Seymour, 2019; Hamilton et al., 2017; Seymour, Rhodes, Stein & Langdon, 2016). Moreover, some studies have reported similar results in unaffected first-degree relative of schizophrenia patients (Green, et al., 1997; Shaqiri et al., 2015), signifying that this deficit may be an endophenotype of schizophrenia spectrum disorders (Berkovitch et al., 2017; Green, Lee, Wynn & Mathis, 2011). Indeed, comparable results have been found in schizotypal samples (Cappe et al., 2012; Park, Lim, Kirk & Waldie, 2015). As opposed to patients' relatives, in a general student population, Cappe and colleagues (2012) reported impaired performance on backward visual masking in participants with high cognitive disorganisation. This was later replicated in an EEG-study, where backward masking in healthy controls, schizophrenia patients and healthy schizotypal cognitive disorganised individuals was assessed (Favrod et al., 2017). In addition to these deficits in masking experiments, the dissociation between impaired conscious and intact subliminal processing in schizophrenia and to a lesser extent, schizotypy, has also become apparent in inattentional and change blindness studies (e.g. Grandgenevere et al., 2015; Hanslmayer et al., 2013; Kreitz, Schnuerch, Gibbons & Memmert, 2015; Laycock, Cutajar & Crewther, 2019; Tschacher, Schuler & Junghan, 2006). Thus, conscious information processing deficits could be positioned on a continuum of cognitive functioning ranging from small anomalies in schizotypy to more severe impairments in schizophrenia patients (Cochrane, Petch & Pickering, 2012). Nevertheless, to understand the nature and implications of this possible continuum, more research in schizotypy is needed.

In summary, based on patient studies and preliminary results in subclinical schizotypal samples, the notion that disruptions in conscious access represent a schizophrenia vulnerability merits further investigation. The nature of the underlying neural mechanisms of these disruptions in conscious access is still under discussion. In general, explanations can be divided into two main ideas. The first one states that conscious information processing deficits stem from a perceptual impairment, in other words an early bottom-up deficiency, whereas the second account poses that the problem arises later on, due to impairments of higher order attentional processes (Berkovitch et al., 2017).

Regarding the first hypothesis, there exists a large amount of literature that demonstrates early sensory processing deficits in schizophrenia and schizotypy, albeit to a lesser extent (Wan, Thomas, Pisipati, Jarvis & Boutros, 2017). Critical evidence comes from EEG research on early sensory gating, i.e. the habituation to repeated stimuli in order to distinguish relevant from unimportant incoming information and determine which sensory signals will be processed (e.g. Park, Lim, Kirk, & Waldie, 2015; Thoma et al., 2017). Indeed, an aberrant assignment of relevance to stimuli could cause an elevated consciousness threshold, as incoming information could be wrongly judged irrelevant and thus not be processed. Interestingly for our hypothesis on the role of noradrenaline in cognitive dysfunctions in schizotypy, animal research suggests that the locus coeruleus, the primary area for noradrenaline synthesis, is of utmost importance in sensory gating (e.g. Fast & McGann, 2017). This theory is further corroborated by a pharmacological study demonstrating that in contrast to a placebo condition, a single dose of clonidine, a α2-noradrenergic agonist, is effective in normalizing the P50 suppression response in schizophrenics (Oranje & Glenthøj, 2014).

In opposition to this bottom-up view, Berkovitch and colleagues (2017) suggest that later, top-down attentional processes might cause the disruption in conscious access. This top-down account relies on the underlying idea that P3b is a marker of conscious perception (Dehaene, Changeux & Naccache, 2011). Beyond the global neuronal workspace theory, P3b is thought to reflect consequences of conscious access (Rutiku et al., 2015). For example, P300 is related to working memory updating and the appraisal of a stimuli in terms of their subjective probability or novelty and motivational importance (Nieuwenhuis, Aston-Jones & Cohen, 2005; Zhao, Zhou & Fu, 2013). In schizophrenia patients, especially the P3b component is consistently found to be attenuated, mainly in response to auditory stimuli (e.g. Bramon et al., 2004; Ford, 1999; Linden, 2005; Umbricht, Bates, Liebermann, Kane & Javitt, 2006). In addition, this finding has been replicated in unaffected family members of schizophrenics, populations at risk for psychosis and subclinical schizotypy samples, although for the later, results are mixed (Bestelmeyer et al., 2009; Kim et al., 2018). For this reason, the auditory P300 is tentatively regarded as a useful biological marker or an endophenotype for schizophrenia (Turetsky et al., 2015). However, in comparative studies which also included bipolar disorder and schizoaffective disorder patients, it was impossible to distinguish all patient groups based on the P300 component alone (Bestelmeyer et al., 2009; Chun et al., 2013).

Accordingly, it has been proposed that the P3b could be a marker of psychosis vulnerability and valuable for predicting the onset of acute psychotic episode (Bramon et al., 2008; Hamilton et al., 2018). As such, it could be expected that P3 abnormalities are associated with the positive factor of schizotypy. Nevertheless, to date, there are few studies on P3 impairments in subclinical schizotypy and even less studies have attempted to uncover the different schizotypy factors in relation to the P3 component. One exception is a study from Kim et al. (2018), in which a correlation with the negative and cognitive component only was found.

To note, as in the first account, the noradrenergic system contributes to this supposed top-down mechanism of conscious processing. Indeed, the locus coeruleus-P3 hypothesis assumes that the P3 mirrors phasic (fast rapid firing of neurons) activity of the noradrenergic system (Nieuwenhuis, Aston-Jones & Cohen, 2005). Hence, investigating the noradrenergic response to unconscious vs conscious perception could be a promising approach to gain a deeper understanding on the role of noradrenaline in schizotypy.

Pupillometry as a method to track locus coeruleus activity and conscious information processing

Locus coeruleus neurons fire in two broad modes: a phasic and a tonic pattern. Phasic firing occurs when high frequency bursts take place for a short period of time (Sara & Bouret, 2012). This mode generally responds to novel or salient sensory input and is implicated in task-related decisions and reward, whereas the tonic discharging mode is not temporally limited and is involved in global levels of arousal and attention (Schwarz & Luo, 2015). Since low tonic firing is associated with drowsiness and high tonic activity promotes exploration of behavioural options, sometimes leading to distractibility, a trade-off is needed for adaptive behaviour (Aston-Jones & Cohen, 2005). In contrast to explorative behaviour, phasic activity corresponds with exploitation, task engagement and specific attention. The adaptive gain theory states that the locus coeruleus' noradrenergic system is crucial for an optimal balance between exploration and exploitation, as it evaluates the value of explorative or exploiting behaviour (Aston-Jones & Cohen, 2005). To measure the behavioural and neural correlates of this trade-off in attention, oddball paradigms are often used. In these experiments, frequent visual or auditory stimuli are presented in most of the trials. On few trials, an equal amount of target or 'oddballs' are presented. Participants are asked to discriminate between these targets and oddballs by ignoring oddballs or

giving a differential response, which requires a certain level of inhibition and flexible attention allocation. In this way, the effect of arousal and saliency, either because of the novelty of a stimulus or its task relevance can be disentangled (Murphy et al., 2011). Some fMRI studies have confirmed the recruitment of the LC and its differences in activation between stimulus types in such paradigms (e.g. Krebs, Park, Bombeke & Boehler, 2018; Murphy et al., 2015).

In schizophrenic patient samples, fMRI auditory oddball studies suggest abnormalities in response to novel oddball stimuli, compared to healthy controls (Collier et al., 2014; Kiehl et al., 2005; Wolf et al., 2008). Additionally, in patients with negative symptoms, one study found an inverse relationship between symptom severity and overactivation in prefrontal areas and the ventral striatum (Wolf et al., 2008). Yet, to date, there is virtually no research with schizotypal samples that assesses noradrenergic, neural or behavioural responses in oddball experiments.

A possibility to study both noradrenergic activity and conscious information processing in oddball paradigms in schizotypy, is pupillometry, the study of pupil size. It has been successfully used in numerous paradigms to capture arousal, attentional processes, conscious perception and mental effort (Mathôt, 2018).

First, pupil size measurements can be used as a proxy of locus coeruleus noradrenaline involvement, given that the pupil dilation response is an involuntary subcortical phenomenon, in part controlled by the noradrenergic system (Costa & Rudebeck, 2016; Laeng et al., 2012; Larsen & Waters, 2018). Whereas the exact nature of the relationship between the locus coeruleus and the iris muscles that control the pupil size remains unclear, animal experiments demonstrated the correspondence in temporal dynamics and amplitude between the phasic firing rates of a single neuron in the locus coeruleus and pupil diameter (Joshi, Kalwani & Gold, 2016; Rajkowski, Kubiak & Aston-Jones, 1993). A series of experiments from Gilzenrat, Nieuwenhuis, Jepma and Cohen (2010) extended on these results, as they presented the similarity between the relationship of human locus coeruleus activity and pupil dilation and the results of earlier animal studies. In addition, it was shown that tonic increases in pupil diameter corresponded with exploration behaviour, i.e. task disengagement. Phasic task related enlargements of pupil size, on the other hand, occurred when task utility, defined by its reward and costs, was high. Their results were as predicted by the adaptive gain theory of locus coeruleus activity

(Aston-Jones & Cohen, 2005; Gilzenrat et al., 2010). In oddball tasks, it was shown that the phasic pupil response is triggered by novel or deviant (oddball) stimuli and appears approximately 1 to 2 seconds post stimulus presentation (Kamp & Donchin, 2014; Murphy et al., 2011). Murphy et al. (2014), using a combined pupillometry – fMRI approach, further corroborated the covariance between pupil dilations and locus coeruleus activity both in resting state and during the oddball task. Following up on these developments pupillary responses have been successfully used to screen for locus coeruleus dysfunctions, for example in subjects at risk for Alzheimer's disease (Elman et al., 2017).

Second, besides their use in estimating attentional responses and tracking the locus coeruleus activity, pupil dilation patterns have proven to be a valuable marker of auditory conscious perception. For example, Kang and Wheatley (2015) used diotically vs. dichotically presented music clips. In dichotic trials participants were asked to attend only one sound. On these dichotic trials, the temporal patterns of pupillary dilations were similar to the pupillary time-courses of trials in which only the attended sound was presented. Employing deconvolution techniques, it was possible to precisely track the temporal dynamics of auditory conscious perception using the pupil dilation responses (Kang & Wheatley, 2015). Furthermore, in a local-global paradigm, where participants had to focus on two types of auditory regularities, it was shown that increases in pupil dilation appeared only on trials where participants were able to consciously report global irregularities in the sound repetition series (Quirins et al., 2018). In addition to this, other authors have proposed that the shifts in attention reflected in pupil dilation responses can be used to infer a preconscious state of perception (Laeng, Sirois & Gredebäck, 2012). As we have described earlier, this is a brief period in which a subject has the ability to consciously access information but is not yet aware of this information (Dehaene, Changeux & Naccache, 2011). It is assumed that the pupil dilation response closely reflects the preconscious to conscious processing transition (Laeng et al., 2012). Indeed, it was shown that the pupil dilations are time-locked to stimuli presentations, prior to subjects reporting the stimuli. Moreover, these pupil responses were independent of sensory changes on the stimuli and only occurred when participants focused on the task and did not engage in mind wandering (Kang, Huffer & Wheatley, 2014; Smallwood et al., 2011). These findings might also be understood from the information theory perspective, which poses that pupil dilation responses are scaled with the amount of information, sensory or internal, being processed at the moment (Zénon, 2019).

Taken together, the pupil dilation response could serve as a sensitive measure of conscious access in the auditory modality. Moreover, the locus coeruleus noradrenergic system seems to underlie this pupillary response.

Research questions and hypotheses

The present study aims to investigate how the noradrenergic system contributes to different stages of conscious and salient information processing in relation to schizotypal traits. To this end, healthy participants with schizotypy scores ranging from minimal to subclinical levels performed a four-condition auditory oddball task (oddball, target, differing from target perceivable at the individual threshold (barely distinguishable), subliminally different from the target (subliminal)), whilst their pupil dilation responses were recorded. The behavioural accuracy on the subliminally differing trials reflect the capacity of conscious access, whereas the phasic pupil dilation on these trials indicate subliminal processing of the stimuli. Trials with barely distinguishable frequencies from the target tones are used to investigate the dynamics of conscious perception in relationship to schizotypy and could be indicative of a preconscious processing state. Hence, this design allows for the operationalisation of the noradrenergic response to novelty, namely the magnitude of the phasic pupil dilation response on oddball trials.

In line with deficits in conscious information access found in schizophrenia and schizotypy (e.g. Berkovitch et al., 2017; Cappe et al., 2012), we hypothesize to find an inverse relationship between behavioural accuracy and schizotypy, more specifically the cognitive disorganisation factor, in a modified 4 condition (standard, task relevant trials; oddball trials; subliminally differing; barely noticeably differing) auditory oddball task. Although research on the associations between the different schizotypy factors (positive, negative, cognitive) is limited, one could assume the relationship between conscious information processing deficits and the cognitive disorganisation component would be the most prominent, as the underlying noradrenaline hypothesis mainly seeks to explicate the cognitive symptom cluster in schizophrenia and by extent, schizotypy (e.g. Maletic et al., 2017; Yamamoto et al., 2014). Moreover, in visual backward masking studies mainly associations with cognitive disorganisation and impaired behavioural performance were found (Cappe et al., 2012; Favrod et al., 2017; Shaqiri et al., 2015).

On the other hand, literature on the top-down hypothesis of impaired conscious access in schizophrenia suggests that the associated P3 marker signifies psychosis, suggesting a possible role for the positive factor in schizotypy (Bramon et al., 2008; Hamilton et al., 2018). Tentatively, in the present study, we hypothesize to find an association with the subscale tapping into the cognitive disorganised factor.

More specifically, we hypothesize that in addition to a lower behavioural accuracy on trials requiring the discrimination of pitch differences either at an individualised threshold or just below, i.e. subliminally different, correct reaction times will be positively associated with cognitive disorganised schizotypy. Given the apparent dissociation between conscious access and intact subliminal and preconscious processing in schizophrenia (Berkovitch et al., 2017, 2018), we hypothesize that there will be significant differences in pupil dilation across trial types (oddball > target (standard) > differing from target at the individual threshold (barely distinguishable) > subliminally different from the target (subliminal)), assuming the pupillary response reflects the amount of sensory information processed, even in a preconscious state (Laeng et al. 2012; Zénon, 2019). Hence, even when behavioural performance in perceiving sensory differences is diminished, we hypothesize that the pupillary response will show the preconscious processing of these differences.

Consequently, based on previous literature reporting hypersensitivity to salient stimuli (e.g. Kiehl et al., 2005; Wolf et al., 2008) in schizophrenic patients, we hypothesize that in a subclinical sample, elevated subclinical cognitive disorganised schizotypy is positively related with the pupillary response to oddball (novel and deviant) trials. Additionally, we aim to explore if an association exists between pitch discrimination abilities and schizotypal traits. As previous literature suggests perceptual difficulties in schizotypy, we expect a negative association between pitch discrimination and schizotypy.

Taken together, we expect to find a deviant noradrenergic response to salience and a reduction in conscious information processing in subclinical cognitive disorganised schizotypy. As schizotypy is regarded a precursor or risk factor in the development of schizophrenic spectrum disorders, replicating difficulties in information processing found in patient samples in healthy individuals might indicate an effect of these deficits in the development of schizophrenic disorders.

Methods

Participants

The study aimed for a sample size of 60 participants. However, due to the COVID-19 outbreak in Belgium in March 2020, there was a limitation to the testing period, which resulted in a final sample of 54 healthy right-handed volunteers aged 18 to 35 (*M*= 24.66; *SD*= 4.12). Participants were recruited through social media and a web platform from the university. Exclusion criteria consisted of non-corrected impaired vision, the use of psychopharmaceuticals and current or past psychological or neurological disorders. Initially all volunteering participants who did not meet exclusion criteria were asked to participate. When about half of the sample size aim was met, a heterogenous purposive sampling approach was used to obtain a greater variability in subclinical schizotypy. All participants were screened using the short version of Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE) (Mason & Claridge, 2005) to assess levels of (sub)clinical schizotypy. During the second part of the recruitment phase, only participants who scored at least 1 standard deviation higher on the cognitive disorganisation subscale, compared to normative population means (Mason & Claridge, 2005), were invited to the lab for testing. All participants provided their written informed consent at the start of the experiment. Participants received €10 or one course credit in turn for their partaking.

Questionnaires and measures

Short Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE; Mason & Claridge, 2005). A shortened version of the O-LIFE, a well validated and reliable self-report instrument that assesses schizotypal personality traits (Burch, Steel, & Hemsley, 1998; Mason & Claridge, 2006), was administered. It consists of 43 yes-no questions divided over four subscales. The items from the unusual experiences subscale (e.g. ‘Are your thoughts sometimes so strong that you can almost heart hem?’) screen for perceptual aberrations, magical thinking, and hallucinations and thus tap into positive schizotypy. The second subscale, cognitive disorganisation (e.g. ‘Do you often have difficulties in controlling your thoughts?’), measures aspects of poor attention, concentration and decision-making, as well as social anxiety. These are characteristics related to thought disorders and disorganized cognitions in psychotic syndromes. Third, the introvertive anhedonia items (e.g. ‘Are there very few things that you have ever enjoyed doing?’) reflect a lack of enjoyment from social and physical pleasure. This subscale score indicates negative schizotypy. Finally, the impulsive nonconformity

questions (e.g. ‘Would you like other people to be afraid of you?’) do not asses schizotypy directly but load on characteristics of questionnaires devised to assess borderline personality disorder and psychoticism (Mason, 1995). This subscale measures impulsive and anti-social behaviour. The internal consistencies of these subscales in our sample were Cronbach α= 0.68, α= 0.83, α= 0.48 and α=0.65, respectively. As our research hypotheses focus on the cognitive disorganisation factor, only the second subscale, with a good internal consistency, was used for formal statistical analysis.

Positive and Negative Affect Schedule (PANAS; Watson, Clark, & Tellegen, 1988). To assess dispositional positive and negative affect, the trait version of the Positive and Negative Affect Schedule was used. It consists of ten items regarding positive affect (PA), for example pride and excitement, and ten items to measure negative affect (NA) such as shame and distress. The internal consistency of these two scores computed for our sample was good (Cronbach α= 0.79 for positive and α= 0.89 for negative affect).

Behavioural inhibition, behavioural activation scales (BIS/BAS; Carver & White, 1994). The BIS/BAS questionnaire is a 20-item scale developed to capture the sensitivity of two emotional systems described by Gray (1990): the behavioural inhibition system (BIS), related to trait anxiety and implicated in behavioural responses to punishment and novelty; and the behavioural activation system (BAS), or trait impulsivity, sensitive to reward and non-punishment. It consists of four subscales: BIS (e.g. ‘I feel pretty worried or upset when I think or know somebody is angry at me’) α= 0.71, BAS drive (e.g. ‘I go out of my way to get things I want’) α= 0.69, BAS fun seeking (e.g. ‘I'm always willing to try something new if I think it will be fun’) α= 0.51 and BAS reward responsiveness (e.g. ‘It would excite me to win a contest’) α= 0.50 . For this study, we were especially interested in the BIS scale and its possible association with schizotypy measures, since in schizophrenia, BIS sensitivity seems to be elevated (Reddy et al., 2014). Moreover, the behavioural expression of the BIS system, i.e. responses to novel events are closely related to functions of the locus coeruleus (Aston-Jones & Cohen, 2005; Krebs et al., 2018).

Experimental Procedure

All participants were tested individually in the department's lab. Before the start of the actual experiment, upon completion of the PANAS and BIS/BAS scales, participants were asked to perform a short pitch discrimination test (Louie, Alsop & Schlaug, 2009). In this way, the auditory oddball task could be adjusted for each individual based on their pitch discrimination abilities. This discrimination task was followed by the set-up of the eye tracker system and the main oddball task. The whole procedure lasted about 30 minutes.

Oddball task

An auditory oddball task was designed in Python using the PsychoPy 3 package (Peirce, 2007). The auditory stimuli were presented over 408 trials, delivered through headphones. The stimuli were presented for 500 ms and consisted of frequent target tones at 500 Hz (80%), infrequent oddball tones (5%) with a randomly picked frequency (either 50 Hz, 100 Hz or 1000 Hz), infrequent subliminally different tones (10%), i.e. differing, either higher or lower, from the target tone with a frequency just smaller than the personal pitch discrimination point, and infrequent barely distinguishable tones (5%) i.e. with a difference in frequency from the target tone set at the level of the individual's pitch discrimination ability. Participants were asked to indicate, within a 2000 ms window after the presentation of each stimulus if the presented tone had the same frequency as the target tone or diverged, by pressing 'j' or 'f' on a keyboard, respectively. Each trial was presented in a pseudorandomized order, under the condition that two or more subsequent oddball trials did not occur. Before beginning the task, participants performed practice trials session to ensure their understanding. Accuracy for every trial was coded as 1 or 0 (1: correct response, 0: no response or incorrect). During the whole task, participants were asked to fix their gaze on a cross presented in the middle of the screen, in order to minimize the confound of gaze position on pupil size.

Pupil size recording and preprocessing

During the oddball task, continuous pupil diameter of the right eye was recorded at a sampling rate of 250 Hz using an Eyelink SR 1000 video-based system, enabling a spatial resolution of 0.01mm. 625 samples per trial were acquired. The experimental room was dimly lit with constant illumination, to avoid influences on the pupil dilation response. Due to unforeseen data loss, the pupillometric data of 30 participants only could be retained for preprocessing and statistical analysis.

The remaining pupil data was preprocessed in R, using the PupilPre package (Kyröläinen, Porretta, van Rij & Järvikivi, 2019). First, missing or samples containing blinks were removed (percentage of data *M*= 8.01, *SD*= 17.97), including a 100 ms buffer immediately before and after each missing sample. Indeed, given that blinks are preceded by a decreased pupil size and followed by a rapid increase, the pupil diameter values surrounding the blinks are distorted (Mathôt et al., 2018). Next, the remaining artefacts were cleaned up using median absolute deviation: the time series of each trial were divided into 100 ms windows and measurements varying more than 2 standard deviations from the 100 ms window's median value were removed. As in the blink removal, the identified extreme windows have 100 ms padding added around them. Within these padded windows multivariate outlier detection was performed by calculating the Mahalanobis multidimensional distributional distance, based on the pupil size and velocity and acceleration of eye movements both on the x-and y axis. This resulted in the detection and removal of 1.99% outliers (*M*= 1.91, *SD*= 1.86).

Each trial lasted for 2500 ms (500 ms auditory stimulus, followed by a 2000 ms response window) and the latency of the pupillary response (Mathôt et al., 2018), the critical window of interest was set from 200 ms to 2500 ms, while a baseline window was determined as the 500 ms prior to tone onset. Afterwards, trials with less than 50% of data points available either in the baseline or critical window were excluded from further analysis. The remaining gaps in the signal were linearly interpolated and filtered using a low-pass first order Butterworth filter (Kret & Sjak-Shie, 2019). The first and last 75 ms of the time series were removed to avoid filtering artefacts. In accordance with the guidelines from Mathôt and colleagues (2018), a baseline subtraction approach was adopted. Hence, pupil measurements for each trial were subtracted from their baseline values. Finally, the average of these values was taken per trial.

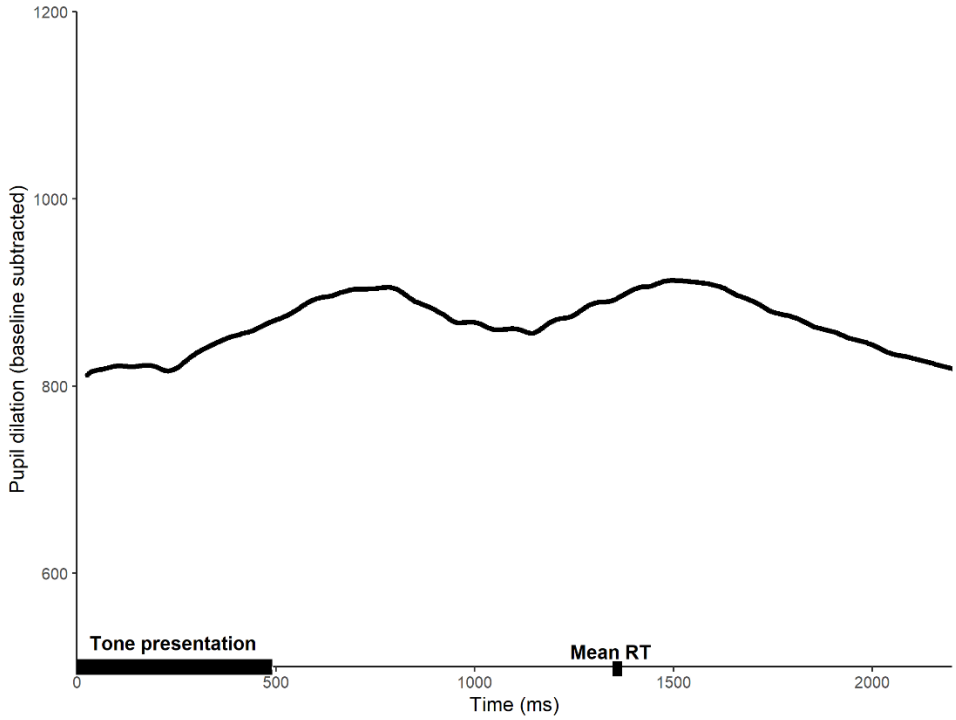

Figure 2: Preprocessed time series, baseline subtracted and averaged over trials

Data analytic plan

All analyses were carried out using R 3.5 (R core team, 2019). First, since various subscales of the questionnaire data violated the normality assumption of Pearson's correlations, Spearman's rho was used to explore possible associations between the schizotypy, personality, affect and pitch discrimination measures. (Generalized) linear mixed effects regression ((G)LMER) was used for all formal analyses, utilizing the lme4 package (Bates, Maechler, Bolker & Walker, 2015). We opted for (generalized) linear mixed models (LMMs) as statistical analysis method because of their superiority in handling unbalanced data (i.e. unbalanced proportion of trial types) and ability to account for interindividual variability in repeated measures responses (Boisgontier & Cheval, 2016), by including random effects.

To test first hypothesis, that cognitive disorganisation in healthy individuals is inversely related to behavioural accuracy on subliminal and barely perceivable trials, a generalized linear mixed model with a binomial family and a logit link function was fitted, with accuracy on each trial (1 or 0) as the dependent variable, condition as a fixed factor (barely, oddball, standard, subliminal), the standardised cognitive

disorganisation subscale as a covariate of interest, and subject as a random intercept. Next, to further investigate behavioural accuracy in relation to disorganised schizotypy, for the subset of accurate trials, a linear mixed model with correct reaction time (in seconds) as the dependent variable, condition as a fixed factor (barely, oddball, standard, subliminal), the standardised cognitive disorganisation subscale as a covariate of interest, and subject as a random intercept was fitted. The assumptions of the linear mixed effects model were checked and appeared violated, hence different generalized linear mixed models using various family and link functions were fitted (i.e. gamma family with log, inverse or identity link functions) and their residual diagnostics of examined using a simulation-based approach (Hartig, 2016). The final model, a GLMER with a gamma distribution and log link function, was selected based on the Akaike information criterion (AIC) comparison of each model.

Next, to test for significant differences in pupil dilation across trial types (oddball > target (standard) > differing from target at the individual threshold (barely distinguishable) > subliminally different from the target (subliminal)) and to examine if cognitive disorganisation was associated with a larger pupillary responses to oddball trials, the baseline subtracted pupillary increase per trial were used as the dependent variable for a linear mixed model, with condition as a fixed factor, cognitive disorganisation as a standardised covariate of interest and subject as a random intercept.

GLMER. The generalized linear mixed models were fit with a Laplace approximation to maximum likelihood. Wald chi-square tests of effects are reported.

LMER. A Restricted maximum likelihood approach was used to fit the aforementioned models. We relied on the 'lmerTest' package to obtain the fixed effects' p-values with the Satterthwaite approximation to degrees of freedom (Kuznetsova, Brockhoff & Christensen, 2017).

Across analyses, the α level was set at 0.05 for all hypothesis testing. The condition factor was sum-coded. Confidence intervals for fixed effects were estimated with the 'confint' function. Pseudo R2 for conditional and marginal effects were estimated with the 'r.squaredGLMM' function from the 'MuMin' package (Barton,& Barton, 2019). All post-hoc tests for the interaction effects (type III), two-sided, were performed using pairwise comparisons of linear trends (slopes) or estimated marginal

means (EMMs), carried out with the ‘emmeans’ package (Length, Singmann & Love, 2018), and corrected for multiple comparisons using Tukey’s method.

Results

Descriptive statistics: short O-LIFE schizotypy subscales

In our sample, elevated scores on unusual experiences and particularly cognitive disorganisation were observed, in contrast to introvertive anhedonia (negative schizotypy) (see Table 1). Hence, there was a high representation of participants with cognitive disorganised traits in the current sample.

Measure	***Mean***	***SD***	***Observed range***	***Scale range***
1. Unusual Experiences	3.48	2.55	0-10	0-12
2. Cognitive Disorganisation	6.30	3.22	0-11	0-11
3. Introvertive Anhedonia	2.22	1.62	0-7	0-10
4. Impulsive Nonconformity	2.72	2.01	0-9	0-10

Table 1: Descriptive statistics for short O-LIFE subscales

Descriptive statistics: associations between trait questionnaires

All associations between the various trait questionnaires can be found in Table 2. The three schizotypy subscales (unusual experiences, cognitive disorganisation and introvertive anhedonia) were positively associated. In line with findings from schizophrenic individuals, the behavioural inhibition system was positively correlated with schizotypy, albeit only with the cognitive disorganisation facet. However, the auditory processing deficits found in schizophrenia and thought disorders (e.g. Dondé et al., 2019; Hamilton et al., 2017) could not be observed in our subclinical schizotypal sample, as no association between pitch discrimination abilities and the cognitive disorganisation subscale was found. Yet, surprisingly, even in our subclinical sample, cognitive disorganisation was strongly related to trait negative affect.

Measure	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*
1. Unusual Experiences		.34 *	.29*	.50***	.04	.39**	-.04	.05
2. Cognitive Disorganisation			.19	.41**	-.27*	.53***	.36**	.14
3. Introvertive Anhedonia				.28*	-.05	.15	-.02	.11
4. Impulsive Nonconformity					-.02	.45***	.12	-.04
5. Positive Affect						-.25	-.43**	-.24
6. Negative Affect							.29*	.09
7. Behavioral inhibition								.08
8. Pitch discrimination (Hz)								

Table 2: Trait questionnaires correlations (Spearman's rho)

*: *Correlation significant at the 0.05 level (2-tailed)*
**: Correlation significant at the 0.01 level (2-tailed)*
****: Correlation significant at the 0.001 level (2-tailed)*

Behavioural outcomes

Oddball accuracy

The GLMER to assess oddball accuracy consisted of the fixed effect factor *condition*, the random intercept for *subject* and the *cognitive disorganisation* covariate. There was a significant main effect of *condition* (barely, oddball, standard, subliminal) $\chi^2(3) = 3219.61$, $p < .001$, but no significant main effect of *cognitive disorganisation* ($b = -0.01$, $SE = 0.17$, $z = -0.02$, $p = .981$). Crucially, there was a significant *condition* x *cognitive disorganisation* interaction effect $\chi^2(3) = 93.78$, $p < .001$. Follow-up tests of the slopes revealed that only for barely distinguishable trials there was an interaction with cognitive disorganisation on accuracy ($b = 0.22$, $SE = 0.05$, $z = 2.37$, 95% CI [0.02; 0.20], $p = .018$), (see Figure 4). Hence, on these trials there was a positive association between levels of *cognitive disorganisation* and accuracy. Further pairwise comparisons indicated that this trend was only significantly different from standard trials ($b = -0.17$, $SE = 0.02$, $z = -7.87$, $p < .001$), all other zs < 2, ps > 0.100. The model (except for the random intercept of *subject*) accounted for 27% of the observed variance in accuracy.

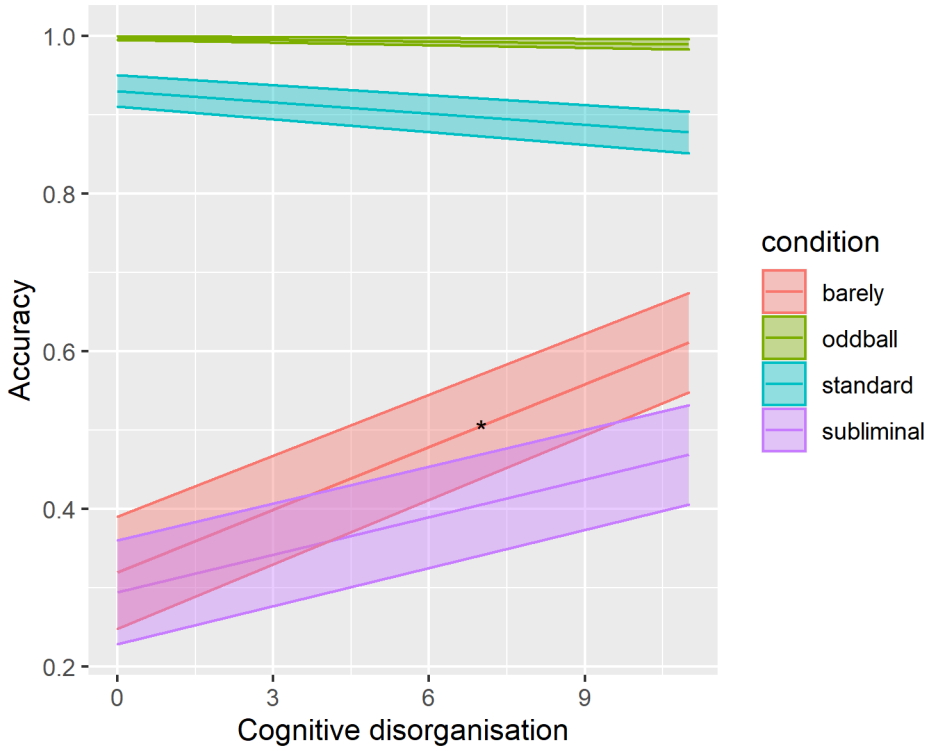

Figure 3: Linear trends for the condition x cognitive disorganisation effect, including standard errors

Fixed Effects					
	Est/Beta	SE	95% CI	z	p
Intercept	1.71	0.16	1.40; 2.02	10.80	<.001
Barely	-1.77	0.09	-1.95; -1.59	-19.24	<.001
Oddball	3.40	0.23	2.93; 3.87	14.28	.001
Standard	0.53	0.08	0.36; 0.69	6.31	<.001
Scale (Cogn. Dis)	-0.00	0.17	-0.33; 0.32	-0.02	.981
Barely: Scale (Cogn. dis)	0.35	0.11	0.15; 0.56	3.23	<.001
Oddball: Scale (Cogn. dis)	-0.40	0.29	-0.96; 0.16	-1.40	.162
Standard: Scale (Cogn. dis)	-0.17	0.10	-0.37; 0.02	-1.76	.079

Random Effects			
	Variance	S.D.	Correlation
Subject (Intercept)	0.99	0.99	
Model fit			
R^2 theoretical	Marginal	Conditional	
	0.27	0.44	
Model equation: glmer ACC ~ Condition * scale (Cogn.Dis) + (1 | Subject), family= binomial (logit)			

Table 3: Model parameters for the oddball accuracy model

Oddball reaction times

For this analysis, only trials with a correct response were considered (79.2% of trials). In addition to the fixed effect factor *condition* and the random *subject* intercept again, *cognitive disorganisation* was included as a fixed covariate of interest. The GLMER demonstrated a significant main effect of *condition* (barely, oddball, standard, subliminal): $\chi^2(3) = 174.94$, $p < .001$. There was no significant main effect of *cognitive disorganisation* ($b = 0.01$, $SE = 0.03$, $t = .31$, $p = .785$), nor a *condition* x *cognitive disorganisation* interaction effect ($\chi^2(3) = 1.56$, $p = .668$).

Post-hoc comparisons of estimated marginal means for the *condition* effect (see Figure 3) indicated that correct response time were the largest for subliminal trials ($b = 0.89$, $SE = 0.03$, 95% CI [0.84; 0.95], $p < .001$) and significantly higher compared to standard (standard/subliminal $b = 0.90$, $SE = 0.01$, $z = -11.16$, $p < .001$) and oddball trials (oddball/ subliminal $b = 0.93$, $SE = 0.01$, $z = -6.06$, $p < .001$) , but not barely distinguishable trials (barely/ subliminal $b = 0.98$, $SE = 0.01$, $z = -1.33$, $p = .545$).[1] This GLMER model (excluding the random subject intercept) accounted for 0.9 % of the observed variance in RT.

[1] Comparisons are represented as ratios, as the model consisted of a log link function

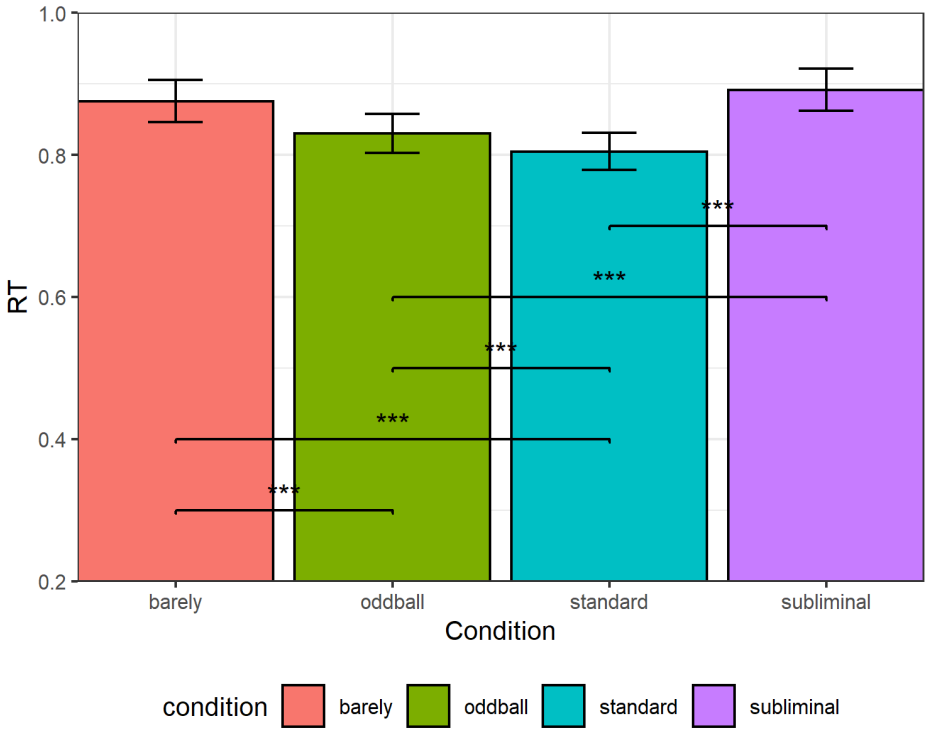

Figure 4: Comparisons of estimated marginal means for the condition on oddball RT

Fixed Effects					
	Est/Beta	SE	95% CI	t	p
Intercept	-0.16	0.03	-0.22; -0.10	-5.029	<.001
Barely	0.03	0.01	0.01; 0.05	3.43	<.001
Oddball	-0.02	0.01	-0.04; -0.01	-3.28	.001
Standard	-0.05	0.01	-0.06; -0.04	-12.22	<.001
Scale (Cogn. Dis)	0.01	0.03	-0.05; 0.08	0.31	.758
Barely: Scale (Cogn.Dis)	-0.01	0.01	-0.03; 0.01	-0.99	.320
Oddball: Scale (Un.exp)	0.01	0.01	-0.01; 0.02	0.93	.353
Standard: Scale (Un.exp)	0.00	0.00	-0.01; 0.01	0.85	.398
Random Effects					

	Variance	S.D.	Correlation
Subject (Intercept)	0.01	0.08	
Model fit			
R^2 lognormal	Marginal	Conditional	
	0.01	0.09	
Model equation: glmer RT ~ Condition * scale (Cogn. Dis) + (1 | Subject) , family= gamma (log)			

Table 4: Model parameters for the oddball reaction times model

Pupil dilation

The final LMER model consisted of the fixed effect factor *condition,* the random *subject* intercept and the fixed *cognitive disorganisation* covariate of interest. There was a significant main effect of *condition* ($F(3, 11962.70) = 25.30$, $p < .001$), whereas the main effect of *cognitive disorganisation* on pupil dilation was non-significant ($b = 32.30$, $SE = 35.44$, $t = 0.91$, $p = .396$). Furthermore, a significant interaction effect of *condition* x *cognitive disorganisation* interaction was found ($F(3, 11963.00) = 4.12$, $p = .006$). However, follow-up tests of the *condition* x *cognitive disorganisation* slopes revealed that this interaction was not statistically significant (ts < 1.60, ps > .120) for any of the trial types(see Figure 5). Yet, pairwise comparisons did indicate a significant difference between the *cognitive disorganisation* slopes on pupil dilation for oddball vs standard trials ($b = -17.09$, $SE = 5.47$, $t = -3.12$, $p = .010$).

As expected, the estimated marginal means comparisons for the main effect of *condition* effect indicated that the pupil dilation was the largest for oddball trials ($b = 999.00$, $SE = 39.2$, 95% CI [920; 1078], $p < .001$). The pupil increase for oddball trials was significantly larger than for the three other conditions: barely ($b = -117.53$, $SE = 22.00$, $t = -5.35$, $p < .001$), standard ($b = -146.13$, $SE = 16.80$, $t = -8.71$, $p < .001$) and subliminal (b= -123.12, $SE = 20.20$, $t = -6.09$, $p < .001$). All other pairwise comparisons were non-significant (ts < -2, ps > .250). The model (except for the random intercept of subject) accounted for 2% of the observed variance in pupil dilation.

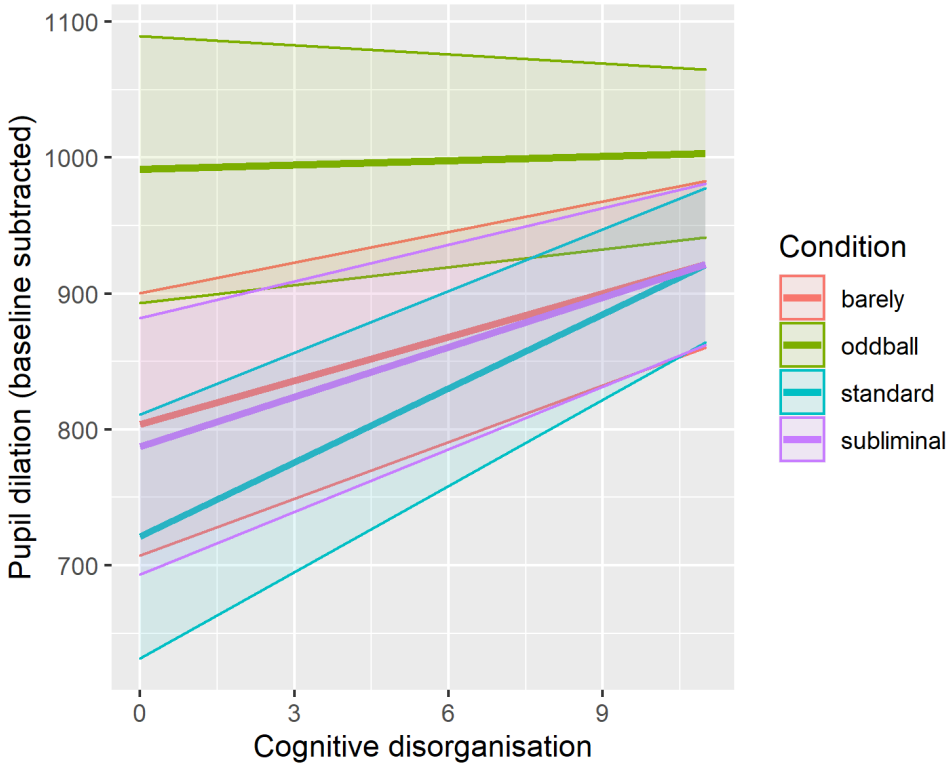

Figure 5: Linear trends for the condition x cognitive disorganisation effect, including standard errors

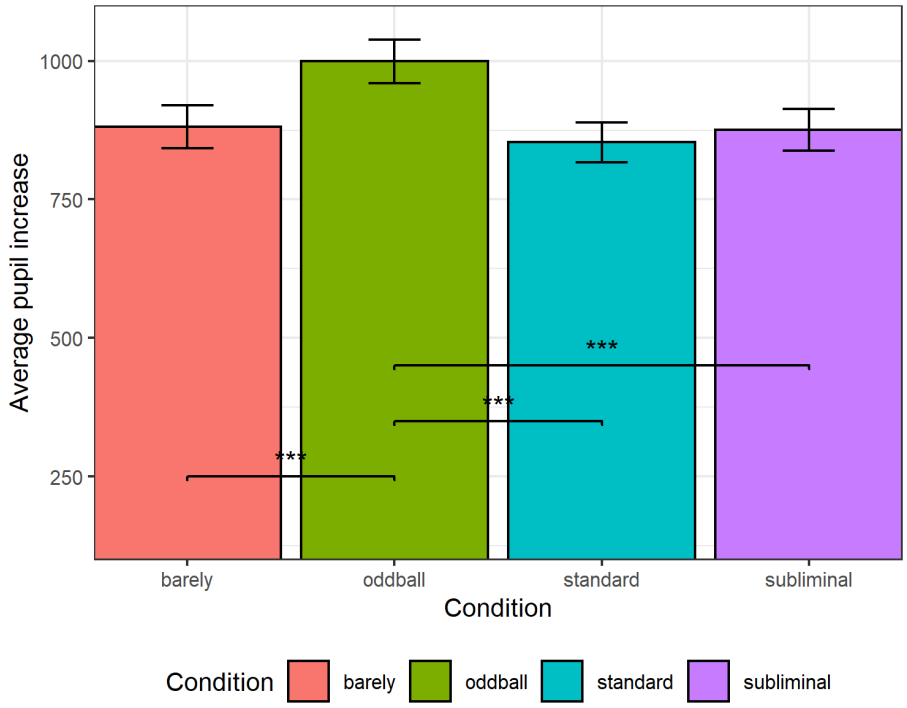

Figure 6: Comparisons of estimated marginal means for the condition effect pupil dilation

Fixed Effects					
	Est/Beta	SE	95% CI	t	p
Intercept	902.39	36.28	831.47; 973.32	24.87	<.001
Barely	-20.84	12.33	-45.00; 3.33	-1.69	.091
Oddball	96.70	13.08	71.07; 122.32	7.39	<.001
Standard	-49.43	7.10	-63.33; -35.53	-6.97	<.001
Scale (Cogn. Dis)	32.30	35.44	-36.98; 101.58	0.91	.370
Barely: Scale (Cogn. dis)	0.57	12.27	-23.46; 24.61	0.05	.963
Oddball: Scale (Cogn. dis)	-29.02	13.08	-54.65; -3.39	-2.22	0.03
Standard: Scale (Cogn. dis)	23.40	7.09	9.51; 37.29	3.30	<.001

Random Effects			
	Variance	S.D.	Correlation
Subject (Intercept)	38244	1195.6	

Model fit		
R^2	Marginal	Conditional
	0.02	0.19

Model equation: lmer Pupilchange ~ Condition * scale (Cogn.Dis) + (1 | Subject)

Table 5: Model parameters for the pupil dilation model

Discussion and conclusion

With the present study, we sought to elucidate the role of the noradrenergic locus coeruleus system in the different stages of conscious and novel information processing in healthy individuals within a range of psychometrically defined schizotypy. In order to disentangle conscious access to information and the preconscious and subliminal processing of sensory stimuli, a combined behavioural – pupillometric oddball experiment was designed.

Concerning the first hypothesis, we expected to find to an inverse relationship between behavioural accuracy and cognitive disorganised schizotypy on trials requiring the discrimination of pitch differences either at an individualised threshold or just below, i.e. subliminally different. Considering the findings of elevated conscious access threshold in schizophrenia and some reports in schizotypy (e.g. Cappe et al., 2012; Favrod et al., 2018), we aimed to replicate these findings with a novel paradigm, in a healthy sample.

As predicted, only on the barely distinguishable trials requiring pitch discrimination at the personal threshold, a statistically significant effect of schizotypy on accuracy was found. Contradictory to our hypothesis, however this was a positive association. If anything, in a subclinical sample, high levels of cognitive disorganised schizotypy seemed to predict an increased ability to consciously report of sensory differences, on the individualised perception limit. This is seemingly in sharp contrast with the predictions of the continuum model in which schizotypy is regarded as a risk-factor in the development of schizophrenic spectrum disorders (e.g. Nelson et al., 2013). Possibly, given that our sample consisted of exclusively healthy individuals, mainly highly educated university students, buffering effects might have been at play. For example, general intelligence is found to be a protective factor against the psychosis risk in schizotypy (Meller et al., 2019). Moreover, it is important to acknowledge that participants with elevated schizotypy in our sample only scored high on the cognitive and/or positive factor. Virtually no participants with negative schizotypy could be included, which might partially explain the unaffected performance. Indeed, as some studies point out, the combination of cognitive disorganised and negative schizotypy is especially associated with negative outcomes in terms of neurocognition and schizophrenia risk, whereas positive schizotypy seems to be more benign (Daly, Afroz & Walder, 2012; Grant & Hennig,

2019). Possibly, by using the university platform our sampling was biased and the pattern of schizotypal traits too homogenous, failing to recruit participants with a more disadvantageous combination of schizotypal traits. Another more theoretical reflection that can be made concerning our sample is the critique on the disorganised construct as a dimension of schizotypy, i.e. a schizophrenia liability. It can be reasoned that disorganisation is a modifying personality construct in the expression of schizophrenia or schizotypal symptoms but does not represent a schizotypy factor by itself (Feigenson, Gara, Roché & Silverstein, 2014). Thus, one could argue that even though our sample scored high on cognitive disorganisation, they did not meet the criteria for schizophrenia liability, given the mainly low scores on the other subscales, which might partially explain why in this population, seemingly no evidence for a noradrenergic dysfunction was found. Although only preliminary, the latter study demonstrated in a general population that highly disorganised individuals did not meet high psychosis risk criteria (Feigenson et al., 2014). Correspondingly, the finding that in the general population, cognitive disorganisation is highly likely to occur in combination with other schizotypy dimensions, could indicate that cognitive disorganisation on itself is not necessarily a separate subtype of schizotypy (Polner et al., 2019).

A possible explanatory mechanism for the improved behavioural performance on trials requiring the detection of very subtle sensory difference in cognitive disorganised schizotypy might lie in aberrant saliency hypothesis (e.g. Haselgrove et al., 2016). Namely, disorganised schizotypy is associated with deficits in distinguishing relevant from unimportant incoming information (Olypher, Klement & Fenton, 2006). Participants were simply told to search for the target tone and encourage to respond on every single trial, hence were not explicitly aware that subliminally different and small deviations in tones would be presented. Thus, in our design one could argue that standard (target) and oddball tones were salient: i.e. task-relevant and novel/ unexpected. The highly cognitive disorganised individuals might have had difficulties with inhibiting the processing of the less relevant, barely differing, and subliminal tones which led to a better performance on those trials specifically. This aberrant saliency is especially related dopamine dysregulations (Kapur, 2003; Galderisi et al., 2018). As aforesaid, it is unlikely that only noradrenergic or dopaminergic dysfunctions underlie schizotypy. Accordingly, future research should attempt to further develop and test an integrative perspective on the role of the two systems (Van Kammen & Kelley, 1991).

However, there are two apparent issues with this dopamine interpretation. First, if a problem in distinguishing relevant information, we might expect a negative effect of cognitive disorganisation on identifying target tones. Second, a smaller pupillary response, suggesting reduced information processing of those tones could be expected. Yet, although post-hoc pairwise comparisons indicated that the linear trend for cognitive disorganisation on accuracy in standard trials was significantly different from the cognitive disorganisation-accuracy correspondence found for barely distinguishable trials, the linear trend for cognitive disorganisation on accuracy in target (standard) trials itself was non-significant. Regarding the second issue, to explore the non-significant association between pupil dilation on target trials and cognitive disorganisation, a Bayesian hypothesis test for the correlation between the average baseline subtracted pupil dilation on standard trials and cognitive disorganisation scores was performed (Wetzels & Wagenmakers, 2012). With a Bayes factor of 0.43, results were inconclusive, with anecdotal evidence in favour of the null hypothesis: i.e. no association between cognitive disorganisation and pupil dilation on target trials.

Moreover, for the subliminally differing trials, which can be regarded as task irrelevant, no positive association between accuracy and cognitive disorganisation was observed. On the contrary, although exploratory, a Bayes factor of 0.21 was calculated for the correlation between the sum of accuracies on subliminal trials and the cognitive disorganisation subscale (Wetzels & Wagenmakers, 2012). This indicates that in our data, there might be substantial evidence in favour of the null hypothesis: no connection between cognitive disorganised schizotypy and accuracy in reporting subliminally different sensory differences. Hence, this exploratory analysis hesitantly provides additional evidence that in our sample, cognitive disorganised schizotypy was not correlated with a heightened threshold for conscious perception of sensory differences.

Based on our second research hypothesis, we expected to find significant differences in pupil dilation across trial types, presuming that the pupillary response reflects the amount of sensory information processed, even in a preconscious state (Laeng et al. 2012; Zénon, 2019). Unsurprisingly, we did find a significant effect of trial type on pupil dilation, with the largest increase for oddball trials. However, no significant differences between the pupillary response to target, barely distinguishable and subliminally different tones was observed. This could indicate that our design was

not sensitive enough to these differences, which was also reflected in the large amount of variance pupil dilation explained by individual differences compared to the task conditions. Similarly, even though a significant interaction effect of cognitive disorganisation and task condition on pupillary response was found, we did not find evidence for our next hypothesis; the positive association between cognitive disorganised schizotypal traits and the pupillary response to oddball (novel and deviant) trials, based on previous literature reporting hypersensitivity to salient stimuli (e.g. Kiehl et al., 2005; Wolf et al., 2008) in schizophrenic patients. Again, the homogeneity of the sample might have played a role. This is possibly in line with the null findings, albeit behaviourally, of positive schizotypy on oddball reaction times in a student population (Gross, Araujo, Zedelius & Schooler, 2019). Likewise, not only did we find no results of psychometrically defined schizotypy on oddball pupillary responses, no statistically significant effect on correct reaction times was found in our study either.

Thus, as we have mentioned, our study faced limitations in terms of sample and the design, although innovative, might be not suited to detect subtle differences in a subclinical population. It is also crucial to note that our paradigm has some dissimilarities compared to previous visual backward masking experiments investigating conscious information processing in schizotypy. Whereas in shine through visual backward masking studies the awareness of the task-relevant stimulus is hindered by presenting a second mask, in our paradigm, the target is unaffected. Furthermore, decreased performance is operationalised as more processing time needed (longer SOA) in the former studies, which corresponds to the accurate reaction times in our study. Indeed, the positive association between cognitive disorganised schizotypy and behavioural performance was found only for the binary accuracies, not for the reaction times needed to respond correctly. Even though no significant effect on reaction times was found, it is possible that our design was not sensitive enough to detect if such longer processing times were needed in our sample. In this aspect, our design could be more similar to inattentional blindness or change blindness studies, related phenomena also taken into consideration in theories of elevated conscious access in schizophrenia and possibly schizotypy (Berkovitch et al., 2017). Those paradigms require the detection of an unexpected event or change in a visual scene. In our task, participants were required to remember the target tone and compare to presented subtle differing sounds, which bears a resemblance with change blindness studies. Remarkably, a large population-based study found no

evidence for schizotypy as a predictor of inattentional blindness (Kreitz, Schnuerch, Gibbons & Memmert, 2015). Perhaps, the information processing deficits in schizotypal healthy populations are more intrinsically related to the task-specific aspects of masking studies than we assumed.

Lastly, due to data loss, the sample size for the pupillometry analysis was rather small. On the other hand, our study had methodological strengths, such as the consideration of schizotypy as a continuous variable, instead of group based or median-split analyses previously used (e.g. Cappe et al., 2012).

To conclude, the current findings further support the continuous and complex nature of schizotypy, in contrast to the notion of schizotypy as one unitary psychosis risk-factor. Future studies should aim for a more heterogeneous sample and address the several patterns of schizotypal trait factors, while taking into account the interplay of schizotypy with additional personality, affect and cognitive factors.

References

Abu-Akel, A., Baxendale, L., Mohr, C., & Sullivan, S. (2018). The association between schizotypal traits and social functioning in adolescents from the general population. *Psychiatry research*, 270, 895-900. doi: 10.1016/j.psychres.2018.11.007

Acosta, H., Straube, B., & Kircher, T. (2018). Schizotypy and mentalizing: an fMRI study. *Neuropsychologia*. doi:10.1016/j.neuropsychologia.2018.11.012

Appels, M.C., Sitskoorn, M.M., Vollema, M.Q., Kahn, R.S., 2004. Elevated levels of schizotypal features in parents of patients with a family history of schizophrenia spectrum disorders. *Schizophrenia Bulletin,* 30 (4) 781-790. doi: 10.1093/oxfordjournals.schbul.a007131

Aston-Jones, G., & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: Adaptive Gain and Optimal Performance. *Annual Review of Neuroscience*, 28(1), 403–450. doi: 10.1146/annurev.neuro.28.061604.135709

Barrantes-Vidal, N., Grant, P., & Kwapil, T. R. (2015). The role of schizotypy in the study of the etiology of schizophrenia spectrum disorders. *Schizophrenia Bulletin*, 41(suppl_2), S408-S416. doi: 10.1093/schbul/sbu191

Barrantes-Vidal, N., Gross, G. M., Sheinbaum, T., Mitjavila, M., Ballespí, S., & Kwapil, T. R. (2013). Positive and negative schizotypy are associated with prodromal and schizophrenia-spectrum symptoms. *Schizophrenia Research*, 145(1-3), 50-55. doi: 10.1016/j.schres.2013.01.007

Berkovitch, L., Dehaene, S., & Gaillard, R. (2017). Disruption of conscious access in schizophrenia. *Trends in cognitive sciences,* 21(11), 878-892. doi: 10.1016/j.tics.2017.08.006

Berkovitch, L., Del Cul, A., Maheu, M., & Dehaene, S. (2018). Impaired conscious access and abnormal attentional amplification in schizophrenia. *NeuroImage: Clinical*, 18, 835-848. doi: 10.1016/j.nicl.2018.03.010

Berridge, C. W., & Waterhouse, B. D. (2003). The locus coeruleus–noradrenergic system: modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews*, 42(1), 33–84. doi:10.1016/s0165-0173(03)00143-7

Bestelmeyer, P. E. G., Phillips, L. H., Crombie, C., Benson, P., & St.Clair, D. (2009). The P300 as a possible endophenotype for schizophrenia and bipolar disorder: Evidence from twin and patient studies. *Psychiatry Research,* 169(3), 212–219. doi: 10.1016/j.psychres.2008.06.035

Bollini, A.M., Compton, M.T., Esterberg, M.L., Rutland, J., Chien, V.H., Walker, E.F. (2007). Associations between schizotypal features and indicators of neurological and morphological abnormalities. *Schizophrenia Research* 92 (1), 32–40. doi: 10.1016/j.schres.2007.01.018

Bramon, E., Rabe-Hesketh, S., Sham, P., Murray, R. M., & Frangou, S. (2004). Meta-analysis of the P300 and P50 waveforms in schizophrenia. *Schizophrenia research*, 70(2-3), 315-329. doi: 10.1016/j.schres.2004.01.004

Bramon, E., Shaikh, M., Broome, M., Lappin, J., Bergé, D., Day, F., ... & Howes, O. (2008). Abnormal P300 in people with high risk of developing psychosis. *Neuroimage,* 41(2),553-560. doi: 10.1016/j.neuroimage.2007.12.038

Burch, G. S. J., Steel, C., & Hemsley, D. R. (1998). Oxford—Liverpool inventory of feelings and experiences: reliability in an experimental population. *British Journal of Clinical Psychology*, 37(1), 107-108. doi: 10.1111/j.2044-8260.1998.tb01284.x

Butler, P. D., & Javitt, D. C. (2005). Early-stage visual processing deficits in schizophrenia. *Current opinion in psychiatry*, 18(2), 151.

Campellone, T. R., Elis, O., Mote, J., Sanchez, A. H., & Kring, A. M. (2016). Negative symptoms in psychometrically defined schizotypy: The role of depressive symptoms. *Psychiatry research*, 240, 181-186. doi: 10.1016/j.psychres.2016.04.020

Cappe, C., Herzog, M. H., Herzig, D. A., Brand, A., & Mohr, C. (2012). Cognitive disorganisation in schizotypy is associated with deterioration in visual backward masking. *Psychiatry Research*, 200(2-3), 652-659. doi: 10.1016/j.psychres.2012.07.001

Caruana, N., Stein, T., Watson, T., Williams, N., & Seymour, K. (2019). Intact prioritisation of unconscious face processing in schizophrenia. *Cognitive neuropsychiatry*, 1-17. doi: 10.1016/j.psychres.2016.04.020

Carver, C. S., & White, T. L. (1994). Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: the BIS/BAS scales. *Journal of personality and social psychology*, 67(2), 319.

Chapman, L. J., & Chapman, J. P. (1978). Revised physical anhedonia scale. Unpublished test, 476-489.

Chapman, L. J., Chapman, J. P., & Raulin, M. L. (1978). Body-image aberration in Schizophrenia. *Journal of abnormal psychology*, 87(4), 399. doi: 10.1037/0021-843X.87.4.399

Charles, L., Gaillard, R., Amado, I., Krebs, M. O., Bendjemaa, N., & Dehaene, S. (2017). Conscious and unconscious performance monitoring: Evidence from patients with schizophrenia. *Neuroimage*, 144, 153-163. doi: 10.1016/j.neuroimage.2016.09.056

Chun, J., Karam, Z. N., Marzinzik, F., Kamali, M., O'Donnell, L., Tso, I. F., ... & Deldin, P. J. (2013). Can P300 distinguish among schizophrenia, schizoaffective and bipolar I disorder? An ERP study of response inhibition. *Schizophrenia research*, 151(1-3), 175-184. doi: 10.1016/j.schres.2013.10.020

Claridge, G. E. (1997). Schizotypy: Implications for illness and health. Oxford University Press.

Claridge, G. & Beech, T. (1995). Fully and quasi-dimensional constructions of schizotypy. *Schizotypal personality*, 29, 192-216.

Cohen, A. S., Mohr, C., Ettinger, U., Chan, R. C. K., & Park, S. (2015). Schizotypy as An Organizing Framework for Social and Affective Sciences. *Schizophrenia Bulletin,* 41(suppl 2), S427–S435. doi: 10.1093/schbul/sbu195

Compton, M. T., Goulding, S. M., Bakeman, R., & McClure-Tone, E. B. (2009). Confirmation of a four-factor structure of the Schizotypal Personality Questionnaire among undergraduate students. *Schizophrenia Research*, 111(1-3), 46-52. doi: 10.1016/j.schres.2009.02.012

Costa, V. D., & Rudebeck, P. H. (2016). More than Meets the Eye: The Relationship between Pupil Size and Locus Coeruleus Activity. *Neuron*, 89(1), 8–10. doi: 10.1016/j.neuron.2015.12.031

Crow, T. J. (1980). Molecular pathology of schizophrenia: more than one disease process?. *British medical journal*, 280(6207), 66. doi: 10.1136/bmj.280.6207.66

Crow, T.J., Baker, H.F., Cross, A.J., Joseph, M.H., Lofthouse, R., Longden, A., Owen, F., Filey, G.J., Glover, V., Killpack, W.S. (1979). Monoamine mechanisms in chronic schizophrenia: post-mortem neurochemical findings. *Br. J. Psychiatry* 134, 249–256. doi: 10.1192/bjp.134.3.249

Daly, M. P., Afroz, S., & Walder, D. J. (2012). Schizotypal traits and neurocognitive functioning among nonclinical young adults. *Psychiatry research*, 200(2-3), 635-640. doi: 10.1016/j.psychres.2012.06.016

Davis, J., Eyre, H., Jacka, F. N., Dodd, S., Dean, O., McEwen, S., … Berk, M. (2016). A review of vulnerability and risks for schizophrenia: Beyond the two hit hypothesis. *Neuroscience & Biobehavioral Reviews*, 65, 185–194. doi:10.1016/j.neubiorev.2016.03.017

De Picker, L. J., Morrens, M., Chance, S. A., & Boche, D. (2017). Microglia and brain plasticity in acute psychosis and schizophrenia illness course: a meta-review. *Frontiers in psychiatr*y, 8, 238. doi: 10.3389/fpsyt.2017.00238

Dehaene, S., Changeux, J. P., & Naccache, L. (2011). The global neuronal workspace model of conscious access: from neuronal architectures to clinical

applications. In *Characterizing consciousness: From cognition to the clinic?* (pp. 55-84). Springer, Berlin, Heidelberg.

Dehaene, S., Changeux, J. P., Naccache, L., Sackur, J., & Sergent, C. (2006). Conscious, preconscious, and subliminal processing: a testable taxonomy. *Trends in cognitive sciences*, 10(5), 204-211. doi: 10.1016/j.tics.2006.03.007

Demjaha, A., Valmaggia, L., Stahl, D., Byrne, M., & McGuire, P. (2012). Disorganization/cognitive and negative symptom dimensions in the at-risk mental state predict subsequent transition to psychosis. *Schizophrenia bulletin*, 38(2), 351-359. doi: 10.1093/schbul/sbq088

Dodell-Feder, D., Saxena, A., Rutter, L., & Germine, L. (2019). The network structure of schizotypal personality traits in a population-based sample. *Schizophrenia research*, 208, 258-267. doi: 10.1016/j.schres.2019.01.046

Dondé, C., Mondino, M., Leitman, D. I., Javitt, D. C., Suaud-Chagny, M. F., D'Amato, T., ... & Haesebaert, F. (2019). Are basic auditory processes involved in source-monitoring deficits in patients with schizophrenia?. *Schizophrenia research*, 210, 135-142. doi: 10.1016/j.schres.2019.05.034

Eckblad, M. L., Chapman, L. J., Chapman, J. P., & Mishlove, M. (1982). The revised social anhedonia scale. Unpublished test.

Eckblad, M., & Chapman, L. J. (1983). Magical ideation as an indicator of schizotypy*. Journal of consulting and clinical psychology*, 51(2), 215-225. Doi: 10.1037/0022-006X.51.2.215

Elman, J. A., Panizzon, M. S., Hagler, D. J., Eyler, L. T., Granholm, E. L., Fennema-Notestine, C., … Kremen, W. S. (2017). Task-evoked pupil dilation and BOLD variance as indicators of locus coeruleus dysfunction. *Cortex*, 97, 60–69. doi: 10.1016/j.cortex.2017.09.025

Ettinger, U., Meyhöfer, I., Steffens, M., Wagner, M., & Koutsouleris, N. (2014). Genetics, cognition, and neurobiology of schizotypal personality: a review of

the overlap with schizophrenia. *Frontiers in psychiatry*, 5, 18. doi: 10.3389/fpsyt.2014.00018

Ettinger, U., Mohr, C., Gooding, D. C., Cohen, A. S., Rapp, A., Haenschel, C., & Park, S. (2015). Cognition and brain function in schizotypy: A selective review. *Schizophrenia Bulletin*, 41(Suppl. 2), S417–S426. doi: 10.1093/schbul/sbu190

Ettinger, U., Williams, S. C., Meisenzahl, E. M., Möller, H. J., Kumari, V., & Koutsouleris, N. (2012). Association between brain structure and psychometric schizotypy in healthy individuals. *The World Journal of Biological Psychiatry*, 13(7), 544-549. doi: 10.3109/15622975.2011.559269

Eysenck, H. J. (1992). The definition and measurement of psychoticism. *Personality and individual differences*, 13(7), 757-785. doi: 10.1016/0191-8869(92)90050-Y

Farley, I. J., Price, K. S., McCullough, E., Deck, J. H., Hordynski, W., & Hornykiewicz, O. (1978). Norepinephrine in chronic paranoid schizophrenia: above-normal levels in limbic forebrain. *Science*, 200(4340), 456-458. doi: 10.1126/science.644310

Fast, C. D., & McGann, J. P. (2017). Amygdalar Gating of Early Sensory Processing through Interactions with Locus Coeruleus. *The Journal of Neuroscience*, 37(11), 3085–3101. doi: 10.1523/jneurosci.2797-16.2017

Favrod, O., Roinishvili, M., da Cruz, J. R., Brand, A., Okruashvili, M., Gamkrelidze, T., ... & Shaqiri, A. (2018). Electrophysiological correlates of visual backward masking in patients with first episode psychosis. *Psychiatry Research: Neuroimaging*, 282, 64-72. doi: 10.1016/j.pscychresns.2018.10.008

Favrod, O., Sierro, G., Roinishvili, M., Chkonia, E., Mohr, C., Herzog, M. H., & Cappe, C. (2017). Electrophysiological correlates of visual backward masking in high schizotypic personality traits participants. *Psychiatry Research*, 254, 251–257. doi: 10.1016/j.psychres.2017.04.051

Feigenson, K. A., Gara, M. A., Roché, M. W., & Silverstein, S. M. (2014). Is disorganization a feature of schizophrenia or a modifying influence: Evidence of covariation of perceptual and cognitive organization in a non-patient sample. *Psychiatry Research*, 217(1–2), 1–8. doi: 10.1016/j.psychres.2014.03.005

Fitzgerald, P. J. (2014). Is elevated norepinephrine an etiological factor in some cases of schizophrenia? *Psychiatry Research*, 215(3), 497–504. doi: 10.1016/j.psychres.2014.01.011

Flückiger, R., Ruhrmann, S., Debbane, M., Michel, C., Hubl, D., Schimmelmann, B. G., ... & Schultze-Lutter, F. (2016). Psychosis-predictive value of self-reported schizotypy in a clinical high-risk sample. *Journal of abnormal psychology*, 125(7), 923. doi: 10.1037/abn0000192

Flückiger, R., Michel, C., Grant, P., Ruhrmann, S., Vogeley, K., Hubl, D., ... & Schultze-Lutter, F. (2019). The interrelationship between schizotypy, clinical high risk for psychosis and related symptoms: Cognitive disturbances matter. *Schizophrenia research*, 210, 188-196. Doi: doi.org/10.1016/j.schres.2018.12.039

Fonseca-Pedrero, E., Chan, R. C., Debbané, M., Cicero, D., Zhang, L. C., Brenner, C., ... & Cohen, A. (2018). Comparisons of schizotypal traits across 12 countries: Results from the International Consortium for Schizotypy Research. *Schizophrenia research*, 199, 128-134. doi: 10.1016/j.schres.2018.03.021

Ford, J. M. (1999). Schizophrenia: the broken P300 and beyond. *Psychophysiology*, 36(6), 667-682. doi: 10.1111/1469-8986.3660667

Frith, C. D. (1979). Consciousness, information processing and schizophrenia. *The British Journal of Psychiatry*, 134(3), 225-235. doi: 10.1192/bjp.134.3.225

Galderisi, S., Mucci, A., Buchanan, R. W., & Arango, C. (2018). Negative symptoms of schizophrenia: new developments and unanswered research questions. *The Lancet Psychiatry*, 5(8), 664-677. doi: 10.1016/S2215-0366(18)30050-6

Gilzenrat, M. S., Nieuwenhuis, S., Jepma, M., & Cohen, J. D. (2010). Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. *Cognitive, Affective, & Behavioral Neuroscience*, 10(2), 252-269. doi: 10.3758/CABN.10.2.252

Gilzenrat, M. S., Nieuwenhuis, S., Jepma, M., & Cohen, J. D. (2010). Pupil diameter tracks changes in control state predicted by the adaptive gain theory of locus coeruleus function. *Cognitive, Affective, & Behavioral Neuroscience*, 10(2), 252-269. doi:10.3758/CABN.10.2.252

Gomes, U. C. R., Shanley, B. C., Potgieter, L., & Roux, J. T. (1980). Noradrenergic overactivity in chronic schizophrenia: evidence based on cerebrospinal fluid noradrenaline and cyclic nucleotide concentrations. *The British Journal of Psychiatry*, 137(4), 346-351. doi: 10.1192/bjp.137.4.346

Grandgenevre, P., Vaiva, G., Boloix, E., Bubrovszky, M., Schwan, R., & Laprevote, V. (2015). Dissociation of explicit and implicit responses during a change blindness task in schizophrenia. *Neuropsychologia*, 71, 11-17. doi: 10.1016/j.neuropsychologia.2015.03.009

Grant, P., Green, M. J., & Mason, O. J. (2018). Models of schizotypy: the importance of conceptual clarity. *Schizophrenia bulletin*, 44(suppl_2), S556-S563. doi: 10.1093/schbul/sby012

Grant, P., & Hennig, J. (in press, 2019). Schizotypy, social stress and the emergence of psychotic-like states-A case for benign schizotypy*?. Schizophrenia Research*. doi: 10.1016/j.schres.2019.10.052

Green, M. F., Lee, J., Wynn, J. K., & Mathis, K. I. (2011). Visual Masking in Schizophrenia: Overview and Theoretical Implications. *Schizophrenia Bulletin*, 37(4), 700–708. doi:10.1093/schbul/sbr051

Green, M. F., Nuechterlein, K. H., & Breitmeyer, B. (1997). Backward masking performance in unaffected siblings of schizophrenic patients: evidence for a vulnerability indicator. Archives of General Psychiatry, 54(5), 465-472. doi:10.1001/archpsyc.1997.01830170091012

Gross, M. E., Araujo, D. B., Zedelius, C. M., & Schooler, J. W. (2019). Is perception the missing link between creativity, curiosity and schizotypy? Evidence from spontaneous eye-movements and responses to auditory oddball stimuli. *NeuroImage*, 116125. doi:10.1016/j.neuroimage.2019.116125

Hamilton, H. K., Williams, T. J., Ventura, J., Jasperse, L. J., Owens, E. M., Miller, G. A., ... & Yee, C. M. (2017). Clinical and cognitive significance of auditory sensory processing deficits in schizophrenia. *American Journal of Psychiatry,* 175(3), 275-283. doi: 10.1176/appi.ajp.2017.16111203

Hamilton, H. K., Williams, T. J., Ventura, J., Jasperse, L. J., Owens, E. M., Miller, G. A., ... & Yee, C. M. (2018). Clinical and cognitive significance of auditory sensory processing deficits in schizophrenia. *American Journal of Psychiatry*, 175(3), 275-283. doi: 10.1176/appi.ajp.2017.16111203

Hamilton, H. K., Woods, S. W., Roach, B. J., Llerena, K., McGlashan, T. H., Srihari, V. H., ... & Mathalon, D. H. (2019). Auditory and visual oddball stimulus processing deficits in schizophrenia and the psychosis risk syndrome: forecasting psychosis risk with P300. *Schizophrenia bulletin*, 45(5), 1068-1080. doi: 10.1093/schbul/sby167.

Hanslmayr, S., Backes, H., Straub, S., Popov, T., Langguth, B., Hajak, G., ... & Landgrebe, M. (2013). Enhanced resting-state oscillations in schizophrenia are associated with decreased synchronization during inattentional blindness. *Human brain mapping*, 34(9), 2266-2275. doi: 10.1002/hbm.22064

Hanson, E., Healey, K., Wolf, D., & Kohler, C. (2010). Assessment of pharmacotherapy for negative symptoms of schizophrenia. *Current psychiatry reports*, 12(6), 563-571. doi: 10.1007/s11920-010-0148-0

Haselgrove, M., Le Pelley, M. E., Singh, N. K., Teow, H. Q., Morris, R. W., Green, M. J., … Killcross, S. (2016). Disrupted attentional learning in high schizotypy: Evidence of aberrant salience. *British Journal of Psychology*, 107(4), 601–624. doi: 10.1111/bjop.12175

Hornykiewicz, O. (1982). Brain catecholamines in schizophrenia—a good case for noradrenaline. *Nature*, 299(5883), 484-486. doi: 10.1038/299484a0

Howes, O., Bose, S., Turkheimer, F., Valli, I., Egerton, A., Stahl, D., ... & McGuire, P. (2011). Progressive increase in striatal dopamine synthesis capacity as patients develop psychosis: a PET study. *Molecular psychiatry*, 16(9), 885. doi: 10.1038/mp.2011.20

Jepma, M., & Nieuwenhuis, S. (2011). Pupil diameter predicts changes in the exploration–exploitation trade-off: Evidence for the adaptive gain theory. *Journal of cognitive neuroscience*, 23(7), 1587-1596. doi: 10.1162/jocn.2010.21548

Joshi, S., Li, Y., Kalwani, R. M., & Gold, J. I. (2016). Relationships between pupil diameter and neuronal activity in the locus coeruleus, colliculi, and cingulate cortex. *Neuron,* 89(1), 221-234. doi: 10.1016/j.neuron.2015.11.028

Kaczorowski, J. A., Barrantes-Vidal, N., & Kwapil, T. R. (2009). Neurological soft signs in psychometrically identified schizotypy. *Schizophrenia research*, 115(2-3), 293-302. doi: 10.1016/j.schres.2009.06.018

Kamp, S. M., & Donchin, E. (2015). ERP and pupil responses to deviance in an oddball paradigm. *Psychophysiology*, 52(4), 460–471. doi: 10.1111/psyp.12378

Kang, O. E., Huffer, K. E., & Wheatley, T. P. (2014). Pupil dilation dynamics track attention to high-level information. *PLoS One*, 9(8), e102463. doi: 10.1371/journal.pone.0102463

Kang, O., & Wheatley, T. (2015). Pupil dilation patterns reflect the contents of consciousness. *Consciousness and Cognition*, 35, 128–135. doi: 10.1016/j.concog.2015.05.001

Kapur, S. (2003). Psychosis as a state of aberrant salience: a framework linking biology, phenomenology, and pharmacology in schizophrenia. *American journal of Psychiatry*, 160(1), 13-23. doi: 10.1176/appi.ajp.160.1.13

Kemali, D., Maj, M., Galderisi, S., Ariano, M. G., & Starace, F. (1990). Factors associated with increased noradrenaline levels in schizophrenic

patients. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, 14(1), 49-59. doi: 10.1016/0278-5846(90)90063-M

Kemp, K. C., Bathery, A. J., Barrantes-Vidal, N., & Kwapil, T. R. (2020). Positive, Negative, and Disorganized Schizotypy Predict Differential Patterns of Interview-Rated Schizophrenia-Spectrum Symptoms and Impairment. *Assessment* (1-12). doi: 10.1177/1073191119900008

Kendler, K. S., McGuire, M., Gruenberg, A. M., & Walsh, D. (1995). Schizotypal symptoms and signs in the Roscommon Family Study: Their factor structure and familial relationship with psychotic and affective disorders. *Archives of General Psychiatry*, 52(4), 296-303. doi:10.1001/archpsyc.1995.03950160046009

Kiehl, K. A., Stevens, M. C., Celone, K., Kurtz, M., & Krystal, J. H. (2005). Abnormal hemodynamics in schizophrenia during an auditory oddball task. *Biological psychiatry*, 57(9), 1029-1040. doi: 10.1016/j.biopsych.2005.01.035

Kim, M., Lee, T. H., Kim, J. H., Hong, H., Lee, T. Y., Lee, Y., ... & Kwon, J. S. (2018). Decomposing P300 into correlates of genetic risk and current symptoms in schizophrenia: An inter-trial variability analysis. *Schizophrenia research*, 192, 232-239. doi: 10.1016/j.schres.2017.04.001

Krebs, R. M., Park, H. R., Bombeke, K., & Boehler, C. N. (2018). Modulation of locus coeruleus activity by novel oddball stimuli. *Brain imaging and behavior*, 12(2), 577-584. https://doi.org/10.1007/s11682-017-9700-4

Kreitz, C., Schnuerch, R., Gibbons, H., & Memmert, D. (2015). Some see it, some don't: Exploring the relation between inattentional blindness and personality factors. *PloS one*, 10(5), e0128158. doi: 10.1371/journal.pone.0128158

Kret, M. E., & Sjak-Shie, E. E. (2019). Preprocessing pupil size data: Guidelines and code. *Behavior research methods*, 51(3), 1336-1342. doi: 10.3758/s13428-018-1075-y

Kwapil, T. R., & Barrantes-Vidal, N. (2014). Schizotypy: Looking back and moving forward. *Schizophrenia Bulletin,* 41(2), S366–S373. doi: 10.1093/schbul/sbu186

Kwapil, T. R., Gross, G. M., Silvia, P. J., Raulin, M. L., & Barrantes-Vidal, N. (2018). Development and psychometric properties of the Multidimensional Schizotypy Scale: A new measure for assessing positive, negative, and disorganized schizotypy. *Schizophrenia research*, 193, 209-217. doi: 10.1016/j.schres.2017.07.001

Laeng, B., Sirois, S., & Gredebäck, G. (2012). Pupillometry: A window to the preconscious*?. Perspectives on psychological science*, 7(1), 18-27. doi: 10.1177/1745691611427305

Larsen, R. S., & Waters, J. (2018). Neuromodulatory correlates of pupil dilation. *Frontiers in neural circuits*, 12, 21. doi: 10.3389/fncir.2018.00021

Laycock, R., Cutajar, E., & Crewther, S. G. (2019). Subclinical high schizotypy traits are associated with slower change detection. *Acta Psychologica*, 195, 80-86. doi: 10.1016/j.actpsy.2019.03.005

Lenzenweger, M. F. (2006). Schizotaxia, schizotypy, and schizophrenia: Paul E. Meehl's blueprint for the experimental psychopathology and genetics of schizophrenia. *Journal of Abnormal Psychology*, 115(2), 195. doi: 10.1037/0021-843X.115.2.195

Lenzenweger, M. F. (2006). Schizotypy an organising framework for schizophrenia research*. Current Directions in Psychological Science,* 15, 162–167. doi: 10.1111/j.1467-8721.2006.00428.x

Lenzenweger, M. F. (2018). Schizotypy, schizotypic psychopathology and schizophrenia. *World Psychiatry*, 17(1), 25-26. doi: 10.1002/wps.20479

Lenzenweger, M. F., & Loranger, A. W. (1989). Detection of familial schizophrenia using a psychometric measure of schizotypy. *Archives of General Psychiatry*, 46(10), 902-907. doi:10.1001/archpsyc.1989.01810100044008

Lewandowski, K. E., Barrantes-Vidal, N., Nelson-Gray, R. O., Clancy, C., Kepley, H. O., & Kwapil, T. R. (2006). Anxiety and depression symptoms in psychometrically identified schizotypy. *Schizophrenia Research,* 83(2–3), 225–235. doi: 10.1016/j.schres.2005.11.024

Linden, D. E. (2005). The P300: where in the brain is it produced and what does it tell us?. *The Neuroscientist*, 11(6), 563-576. doi: 10.1177/1073858405280524

Linscott, R. J., & Morton, S. E. (2017). The latent taxonicity of schizotypy in biological siblings of probands with schizophrenia. *Schizophrenia bulletin*, 44(4), 922-932. doi: 10.1093/schbul/sbx143

Linscott, R. J., & Van Os, J. (2013). An updated and conservative systematic review and meta-analysis of epidemiological evidence on psychotic experiences in children and adults: on the pathway from proneness to persistence to dimensional expression across mental disorders. *Psychological medicine*, 43(6), 1133-1149. doi: 10.1017/S0033291712001626

Lohse, M., & Overgaard, M. (2019). Emotional priming depends on the degree of conscious experience*. Neuropsychologia*, 128, 96-102. doi: 10.1016/j.neuropsychologia.2017.10.028

Loui, P., Alsop, D., & Schlaug, G. (2009). Tone deafness: a new disconnection syndrome?. *Journal of Neuroscience*, 29(33), 10215-10220. doi: 10.1523/JNEUROSCI.1701-09.2009

Maletic, V., Eramo, A., Gwin, K., Offord, S. J., & Duffy, R. A. (2017). The role of norepinephrine and its α-adrenergic receptors in the pathophysiology and treatment of major depressive disorder and schizophrenia: a systematic review. *Frontiers in psychiatry*, 8, 42. doi: 10.3389/fpsyt.2017.00042

Mason, O., & Claridge, G. (2006). The Oxford-Liverpool Inventory of Feelings and Experiences (O-LIFE): further description and extended norms. *Schizophrenia researc*h, 82(2-3), 203-211. doi: 10.1016/j.schres.2005.12.845

Mason, O., Claridge, G., Jackson, M., 1995. New scales for the assessment of schizotypy. *Personality and Individual Differences*. 18, 7 – 13. doi: 10.1016/0191-8869(94)00132-C

Mason, O., Linney, Y., & Claridge, G. (2005). Short scales for measuring schizotypy. *Schizophrenia Research*, 78, 293-296. doi: 10.1016/j.schres.2005.06.020

Mata, I., Gilvarry, C. M., Jones, P. B., Lewis, S. W., Murray, R. M., & Sham, P. C. (2003). Schizotypal personality traits in nonpsychotic relatives are associated with positive symptoms in psychotic probands. *Schizophrenia Bulletin*, 29(2), 273-283.7 doi: 10.1093/oxfordjournals.schbul.a007004

Mathôt, S. (2018). Pupillometry: Psychology, Physiology, and Function. *Journal of Cognition*, 1(1): 16, pp. 1–23. doi: 10.5334/joc.18

Mathôt, S., Fabius, J., Van Heusden, E., & Van der Stigchel, S. (2018). Safe and sensible preprocessing and baseline correction of pupil-size data. *Behavior research methods*, 50(1), 94-106. doi: 10.3758/s13428-017-1007-2

McCutcheon, R. A., Abi-Dargham, A., & Howes, O. D. (2019). Schizophrenia, dopamine and the striatum: from biology to symptoms. *Trends in neurosciences*, 42(3), 205-220. doi: 10.1016/j.tins.2018.12.004

Meehl, P. E. (1962). Schizotaxia, schizotypy, schizophrenia. *American Psychologis*t, 17(12), 827–838. doi: 10.1037/h0041029

Meehl, P. E. (1990). Toward an integrated theory of schizotaxia, schizotypy, and schizophrenia. *Journal of Personality Disorders*, 4(1), 1-99. doi: 10.1521/pedi.1990.4.1.1

Meller, T., Ettinger, U., Grant, P., & Nenadić, I. (2019). The association of striatal volume and positive schizotypy in healthy subjects: intelligence as a moderating factor. *Psychological medicine*, 1-9. doi: 10.1017/S0033291719002459

Miyamoto, S., Miyake, N., Jarskog, L. F., Fleischhacker, W. W., & Lieberman, J. A. (2012). Pharmacological treatment of schizophrenia: a critical review of the

pharmacology and clinical effects of current and future therapeutic agents. *Molecular psychiatry*, 17(12), 1206-1227. doi: 10.1038/mp.2012.47

Mohr, C., & Ettinger, U. (2014). An overview of the association between schizotypy and dopamine. *Frontiers in psychiatry*, 5, 184. doi: 10.3389/fpsyt.2014.00184

Moritz, S., Fricke, S., Jacobsen, D., Kloss, M., Wein, C., Rufer, M., ... & Hand, I. (2004). Positive schizotypal symptoms predict treatment outcome in obsessive–compulsive disorder. *Behaviour Research and Therapy,* 42(2), 217-227. doi: 10.1016/S0005-7967(03)00120-7

Murphy, P. R., O'Connell, R. G., O'Sullivan, M., Robertson, I. H., & Balsters, J. H. (2014). Pupil diameter covaries with BOLD activity in human locus coeruleus. Human brain mapping, 35(8), 4140-4154. doi: 10.1002/hbm.22466

Murphy, P. R., Robertson, I. H., Balsters, J. H., & O'connell, R. G. (2011). Pupillometry and P3 index the locus coeruleus–noradrenergic arousal function in humans*. Psychophysiology*, 48(11), 1532-1543. doi: 10.1111/j.1469-8986.2011.01226.x

Nelson, M. T., Seal, M. L., Pantelis, C., & Phillips, L. J. (2013). Evidence of a dimensional relationship between schizotypy and schizophrenia: a systematic review. *Neuroscience & Biobehavioral Reviews*, 37(3), 317-327. doi: 10.1016/j.neubiorev.2013.01.004

Nieuwenhuis, S., Aston-Jones, G., & Cohen, J. D. (2005). Decision making, the P3, and the locus coeruleus--norepinephrine system*. Psychological bulletin,* 131(4), 510. doi: 10.1037/0033-2909.131.4.510

Noguchi, H., Hori, H., & Kunugi, H. (2008). Schizotypal traits and cognitive function in healthy adults. *Psychiatry Research*, 161(2), 162–169. doi: 10.1016/j.psychres.2007.07.023

Oliver, D., Reilly, T. J., Baccaredda Boy, O., Petros, N., Davies, C., Borgwardt, S., ... & Fusar-Poli, P. (2020). What causes the onset of psychosis in individuals at clinical high risk? A meta-analysis of risk and protective factors. *Schizophrenia bulletin*, 46(1), 110-120. doi: 10.1093/schbul/sbz039

Olypher, A. V., Klement, D., & Fenton, A. A. (2006). Cognitive disorganization in hippocampus: A physiological model of the disorganization in psychosis. *Journal of Neuroscienc*e, 26(1), 158 168.doi: 10.1523/JNEUROSCI.2064-05.2006

Oranje B, Glenthoj BY. Clonidine normalizes levels of P50 gating in patients with schizophrenia on stable medication. *Schizophrenia Bulletin* (2014) 40(5):1022–9. doi:10.1093/schbul/sbt144

Park, H. R., Lim, V. K., Kirk, I. J., & Waldie, K. E. (2015). P50 sensory gating deficits in schizotypy. *Personality and Individual Differences*, 82, 142-147. doi: 10.1016/j.paid.2015.03.025

Peirce, J. W. (2007). PsychoPy—psychophysics software in Python. *Journal of neuroscience methods*, 162(1-2), 8-13. doi: 10.1016/j.jneumeth.2006.11.017

Polner, B., Faiola, E., Urquijo, M. F., Meyhöfer, I., Steffens, M., Rónai, L., … Ettinger, U. (2019). The network structure of schizotypy in the general population. *European Archives of Psychiatry and Clinical Neuroscience*, 1-11. doi: 10.1007/s00406-019-01078-x

Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H. Chil- dren's self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Arch Gen Psychiatry* (2000) 57:1053–8. doi:10.1001/archpsyc.57.11.1053

Quirins, M., Marois, C., Valente, M., Seassau, M., Weiss, N., El Karoui, I., ... & Naccache, L. (2018). Conscious processing of auditory regularities induces a pupil dilation. *Scientific reports*, 8(1), 14819. doi: 10.1038/s41598-018-33202-7

Racioppi, A., Sheinbaum, T., Gross, G. M., Ballespí, S., Kwapil, T. R., & Barrantes-Vidal, N. (2018). Prediction of prodromal symptoms and schizophrenia-spectrum personality disorder traits by positive and negative schizotypy: A 3-year prospective study. *PLoS ONE*, 13(11), 1–18. doi: 10.1371/journal.pone.0207150

Rado, S. (1953). Dynamics and classification of disordered behavior. *American Journal of Psychiatry*, 110(6), 406–416.doi:10.1176/ajp.110.6.406

Rajkowski, J., Kubiak, P., & Aston-Jones, G. (1993). Correlations between locus coeruleus (LC) neural activity, pupil diameter and behavior in monkey support a role of LC in attention. *Society of Neuroscience Abstracts*, 19, 974

Reddy, L. F., Green, M. F., Rizzo, S., Sugar, C. A., Blanchard, J. J., Gur, R. E., ... & Horan, W. P. (2014). Behavioral approach and avoidance in schizophrenia: an evaluation of motivational profiles. *Schizophrenia research*, 159(1), 164-170. doi: 10.1016/j.schres.2014.07.047

Rosell, D. R., Futterman, S. E., McMaster, A., & Sever, L. J. (2014). Schizotypal Personality Disorder: A Current Review. *Current Psychiatry Reports*, 16(7). doi:10.1007/s11920-014-0452-1

Rutiku, R., Martin, M., Bachmann, T., & Aru, J. (2015). Does the P300 reflect conscious perception or its consequences?. *Neuroscience*, 298, 180-189. doi: 10.1016/j.neuroscience.2015.04.029

Sara, S. J. (2015). Locus coeruleus in time with the making of memories. *Current Opinion in Neurobiology*, 35, 87–94. doi: 10.1016/j.conb.2015.07.004

Sass, L. A., & Parnas, J. (2003). Schizophrenia, Consciousness, and the Self. *Schizophrenia Bulletin*, 29(3), 427–444. doi:10.1093/oxfordjournals.schbul.a0070

Schwarz, L. A., & Luo, L. (2015). Organization of the locus coeruleus-norepinephrine system. *Current Biology,* 25(21), R1051–R1056. doi: 10.1016/j.cub.2015.09.039

Shaqiri, A., Willemin, J., Sierro, G., Roinishvili, M., Iannantuoni, L., Rürup, L., … Mohr, C. (2015). Does chronic nicotine consumption influence visual backward masking in schizophrenia and schizotypy? *Schizophrenia Research: Cognition*, 2(2), 93–99. doi: 10.1016/j.scog.2015.04.006

Seeman, P. (2004). Atypical antipsychotics: mechanism of action. *Focus,* 47(1), 27-58.

Seymour, K., Rhodes, G., Stein, T., & Langdon, R. (2016). Intact unconscious processing of eye contact in schizophrenia. *Schizophrenia research: cognition*, 3, 15-19. 10.1016/j.scog.2015.11.001

Siddi, S., Petretto, D. R., & Preti, A. (2017). Neuropsychological correlates of schizotypy: a systematic review and meta-analysis of cross-sectional studies. *Cognitive Neuropsychiatry*, 22(3), 186–212. doi:10.1080/13546805.2017.1299702

Smallwood, J., Brown, K. S., Tipper, C., Giesbrecht, B., Franklin, M. S., Mrazek, M. D., ... & Schooler, J. W. (2011). Pupillometric evidence for the decoupling of attention from perceptual input during offline thought. *PloS one,* 6(3), e18298. doi: 10.1371/journal.pone.0018298

Sobin, C., Blundell, M. L., Weiller, F., Gavigan, C., Haiman, C., & Karayiorgou, M. (2000). Evidence of a schizotypy subtype in OCD. *Journal of Psychiatric Research*, 34(1), 15-24. doi: 10.1016/S0022-3956(99)00023-0

Soliman, A., O'driscoll, G. A., Pruessner, J., Holahan, A. L. V., Boileau, I., Gagnon, D., & Dagher, A. (2008). Stress-induced dopamine release in humans at risk of psychosis: a [11 C] raclopride PET study. *Neuropsychopharmacology*, 33(8), 2033. doi: 10.1038/sj.npp.1301597

Steffens, M., Meyhöfer, I., Fassbender, K., Ettinger, U., & Kambeitz, J. (2018). Association of Schizotypy With Dimensions of Cognitive Control: A Meta-Analysis. *Schizophrenia Bulletin*. doi:10.1093/schbul/sby030

Stein, L., & Wise, C. D. (1971). Possible etiology of schizophrenia: Progressive damage to the noradrenergic reward system by 6-hydroxydopamine. *Science*, 171(3975), 1032-1036. doi: 10.1126/science.171.3975.1032

Swanson, L.W. (1976). The locus coeruleus: a cytoarchitectonic, Golgi and immunohistochemical study in the albino rat. *Brain Research*. 110, 39–56. doi: 10.1016/0006-8993(76)90207-9

Terevnikov, V., Joffe, G., & Stenberg, J. H. (2015). Randomized controlled trials of add-on antidepressants in schizophrenia. *International Journal of Neuropsychopharmacology*, 18(9). doi: 10.1093/ijnp/pyv049

Thoma, R. J., Meier, A., Houck, J., Clark, V. P., Lewine, J. D., Turner, J., … Stephen, J. (2017). Diminished auditory sensory gating during active auditory verbal hallucinations. *Schizophrenia Research,* 188, 125–131. doi:10.1016/j.schres.2017.01.023

Tschacher, W., Schuler, D., & Junghan, U. (2006). Reduced perception of the motion-induced blindness illusion in schizophrenia. *Schizophrenia research*, 81(2-3), 261-267. doi: 10.1016/j.schres.2005.08.012

Turetsky, B. I., Dress, E. M., Braff, D. L., Calkins, M. E., Green, M. F., Greenwood, T. A., ... & Radant, A. D. (2015). The utility of P300 as a schizophrenia endophenotype and predictive biomarker: clinical and socio-demographic modulators in COGS-2. *Schizophrenia research*, 163(1-3), 53-62. doi: 10.1016/j.schres.2014.09.024

Umbricht, D. S., Bates, J. A., Lieberman, J. A., Kane, J. M., & Javitt, D. C. (2006). Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia. *Biological psychiatry*, 59(8), 762-772. doi: 10.1016/j.biopsych.2005.08.030

Uys, M. M., Shahid, M., & Harvey, B. H. (2017). Therapeutic potential of selectively targeting the α2C-adrenoceptor in cognition, depression, and schizophrenia—new developments and future perspective*. Frontiers in psychiatry*, 8, 144. doi: 10.3389/fpsyt.2017.00144

Van Kammen, D. P., & Kelley, M. (1991). Dopamine and norepinephrine activity in schizophrenia: An intergrative perspective. *Schizophrenia Research,* 4(2), 173-191. doi: 10.1016/0920-9964(91)90032-M

Vollema, M. G., & van den Bosch, R. J. (1995). The multidimensionality of schizotypy. *Schizophrenia bulletin*, 21(1), 19-31. doi: 10.1093/schbul/21.1.19

Wadenberg, M.-L., Wiker, C., & Svensson, T. H. (2006). Enhanced efficacy of both typical and atypical antipsychotic drugs by adjunctive α2 adrenoceptor blockade: experimental evidence. *The International Journal of Neuropsychopharmacology,* 10(02), 191. doi:10.1017/s1461145706006638

Wan, L., Thomas, Z., Pisipati, S., Jarvis, S. P., & Boutros, N. N. (2017). Inhibitory deficits in prepulse inhibition, sensory gating, and antisaccade eye movement in schizotypy. *International Journal of Psychophysiology*, 114, 47–54. doi:10.1016/j.ijpsycho.2017.02.003

Wang, Y., Ettinger, U., Meindl, T., & Chan, R. C. (2018). Association of schizotypy with striatocortical functional connectivity and its asymmetry in healthy adults. *Human brain mapping*, 39(1), 288-299. doi: 10.1002/hbm.23842

Wetzels, R., & Wagenmakers, E. J. (2012). A default Bayesian hypothesis test for correlations and partial correlations. *Psychonomic Bulletin and Review*, 19(6), 1057–1064. doi: 10.3758/s13423-012-0295-x

Winkelman, N. W. (1954). Chlorpromazine in the treatment of neuropsychiatric disorders. *Journal of the American Medical Association*, 155(1), 18-21. doi:10.1001/jama.1954.03690190024007

Wise, C. D., Baden, M. M., & Stein, L. (1975). Post-mortem measurement of enzymes in human brain: evidence of a central noradrenergic deficit in schizophrenia. In *Catecholamines and Schizophrenia* (pp. 185-198). Pergamon.

Wolf, D. H., Turetsky, B. I., Loughead, J., Elliott, M. A., Pratiwadi, R., Gur, R. E., & Gur, R. C. (2008). Auditory Oddball fMRI in Schizophrenia : Association of Negative Symptoms with Regional Hypoactivation to Novel Distractors, *Brain Imaging and Behavior* 2: 132–145. doi: 10.1007/s11682-008-9022-7

Woodward, N. D., Purdon, S. E., Meltzer, H. Y., & Zald, D. H. (2005). A meta-analysis of neuropsychological change to clozapine, olanzapine, quetiapine, and risperidone in schizophrenia. *International Journal of Neuropsychopharmacology*, 8(3), 457-472. doi: 10.1017/S146114570500516X

Xing, B., et al., Norepinephrine versus dopamine and their interaction in modulating synaptic function in the prefrontal cortex. *Brain Research* (2016) doi: 10.1016/j.brainres.2016.01.005

York, D. H. (1972). Dopamine receptor blockade—a central action of chlorpromazine on striatal neurones. *Brain research*, 37(1), 91-99. doi: 10.1016/0006-8993(72)90348-4

Zénon, A. (2019). Eye pupil signals information gain. *Proceedings of the Royal Society B*, 286(1911), 20191593. doi: 10.1098/rspb.2019.1593

Zhao, X., Zhou, R., & Fu, L. (2013). Working memory updating function training influenced brain activity. *PLoS One*, 8(8), e71063. doi: 10.1371/journal.pone.0071063