Sensory gating is related to positive and disorganised schizotypy in contrast to smooth pursuit eye movements and latent inhibition

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Keywords

Schizophrenia; schizotypy; schizotypal personality; latent inhibition; smooth pursuit eye movements; sensory gating; endophenotypes

Number of words in the abstract=118
Number of words in the main text=8467
Number of figures=8
Number of tables=1

Abstract

Since the characteristics and symptoms of both schizophrenia and schizotypy are manifested heterogeneously, it is possible that different endophenotypes and neurophysiological measures (sensory gating and smooth pursuit eye movement errors) represent different clusters of symptoms. Participants (*N*=205) underwent a standard conditioned-pairing paradigm to establish their sensory gating ratio, a smooth-pursuit eye-movement task, a latent inhibition task, and completed the Schizotypal Personality Questionnaire. A Multidimensional Scaling analysis revealed that sensory gating was related to positive and disorganised dimensions of schizotypy. Latent inhibition and prepulse inhibition were not related to any dimension of schizotypy. Smooth pursuit eye movement error was unrelated to sensory gating and latent inhibition, but was related to negative dimensions of schizotypy. Our findings suggest that the symptom clusters associated with two main endophenotypes are largely independent. To fully understand symptomology and outcomes of schizotypal traits, the different subtypes of schizotypy (and potentially, schizophrenia) ought to be considered separately rather than together.

Sensory gating is related to positive and disorganised schizotypy in contrast with smooth pursuit eye movements and latent inhibition

Schizotypy refers to a set of traits that are highly related to symptoms of schizophrenia (Claridge & Beech, 1995). Though schizotypy rarely includes full-blown psychotic episodes, it can represent an underlying vulnerability to clinical schizophrenia (Barrantes-Vidal, Gross, Sheinbaum, Mitjavila, Ballespí, & Kwapil, 2013). Schizotypal traits exist in the general population (David, 2010; Myles, Rossell, Phillipou, Thomas, & Gurvich, 2017), with extreme levels of them potentially contributing to the diagnosis of schizotypal personality disorder and schizophrenia, and can be categorised into three symptom clusters: positive (e.g., hallucinations and paranoid delusions), negative (e.g., diminished affect, anhedonia and social withdrawal) and disorganised (e.g., bizarre or disorganised thoughts, speech and behaviours; American Psychological Association APA, 2003, Nelson, Seal, Pantelis, & Philips, 2013). Current diagnostic tools use signs of illness to place individuals into distinct, non-overlapping categories. Such tools do not account for the vastly heterogeneous nature of illness, in terms of the presence and severity of symptoms and deficits (Kwapil & Barrantes-Vidal, 2015). Given the high heritability of schizophrenia (Cannon, Kaprio, Lönnqvist, Huttunen, & Koskenvou, 1998; van Dongen, & Boomsma, 2013) and schizotypy (Ericson, Tuvblad, Raine, Young-Wolff, & Baker, 2011; Linney, Murray, Peters, MacDonald, Rijsdijk, & Sham, 2003; Mokhtari, et al., 2016; but see MacDonald III, Pogue-Geile, Debski, & Manuck, 2001), such different presentations of schizotypy may reflect either the action of different genes or different environmental influences (Ericson et al., 2011; Lin, Su, Kuo, Hsiao, Soong, & Chen, 2007).

High levels of schizotypy correlate with similar behavioural, cognitive, neuropsychological, and neurocognitive function deficits as those in people with schizophrenia (Ettinger, Meyhofer, Steffens, Wagner & Koutsouleris, 2014; Fioravanti, Bianchi & Cinti, 2012; Hazlett, Rothstein, Ferreira, Silverman, Siever, & Olincy, 2015) and lead to impaired social and educational abilities (Ettinger, Meyhöfer, Steffens, Wagner, & Koutsouleris, 2014). These behaviours highlight the need for better

understanding of the cognitive impairments associated with schizotypy to aid in the design and implementation of effective interventions (Ettinger, et al., 2014). Indeed, the Diagnostics and Statistical Manual-V (American Psychiatric Association, 2013) considers schizophrenia to be on a continuum[1], with chronic impairments on one end and subtle impairments, schizotypy, and mild perceptual distortions on the other, consistent with Eysenck and Eysenck's (1976) conceptualisation of personality. Studying schizotypy holds the potential to increase our understanding of the etiology and early signs of schizophrenia (Cadenhead, Light, Geyer, McDowell, & Braff, 2002; Miller et al., 2003) with implications for prevention, diagnosis, and treatment (Addington et al., 2015). Research on nonclinical schizotypy also avoids limited experimental control due to medication and hospitalisation associated with a clinical sample of those with schizophrenia (Ettinger, Mohr, Gooding, Cohen, Rapp, Haenschel, & Park, 2015). Therefore, this study will use a non-clinical population, to increase understanding of the cognitive deficits associated with schizotypal traits in a healthy population (Keefe, & Fenton, 2007). Increasingly, researchers are investigating endophenotypes of schizophrenia and schizotypy due to their potential to increase understanding of the neural basis of abnormalities leading to clinical symptoms (Gur, Calkins, Gur, Horan, Nuechterlein, Seidman, & Stone, 2007). Endophenotypes are believed to be stable and reliable manifestations of the underlying genetics of a disorder that relate to or co-occur with the disease's pathology (Braff, Schork, & Gottesman, 2007; Gottesma, & Gould, 2003), and show high levels of heritability (Holzman, Proctor, & Hughes, 1973; Holzman, Proctor, Levy, Yasillo, Meltzer, & Hurt, 1974; Levy, Holzman, Matthysse, & Mendell, 1993). These basic characteristics are considered to be indicators of a genetic or biological vulnerability to developing a physical or psychological disease (Greenwood et al., 2012), even in the absence of any visible diagnosable pathology (Johannesen, O'Donnell, Shekhar, McGrew & Hetrick, 2013). Each endophenotype is driven by a different gene set and may, therefore, reflect different presentations of schizophrenia given the lack of correlation between them (Ivleva, et al., 2014; Thaker, 2008). Of

[1] The dimensional view of schizophrenia is contrasted with the schizotaxia hypothesis (Meehl, 1989), in which schizogenic genes cause a distinct disorder, however, the current psychiatric view favours the dimensional view (American Psychiatric Association, 2013; Nelson, et al., 2013).

course, it is possible that through pleiotropy, an abnormality in a single gene might cause a myriad of phenotypic traits through its effect on proteins that affect multiple systems and traits (Costas, 2018). In this study, we focus on sensory gating, smooth pursuit eye movements, prepulse inhibition, and deviance detection, as four of the most heritable of endophenotypes of schizotypy and probe their respective heterogeneity of symptomology (Adler, Freedman, Ross, Olincy, & Waldo, 1999; Calkins, & Iacono, 2000; Holzman, et al., 2014; Kathmann, Hochrein, Uwer, & Bondy, 2014; Nkam, Bocca, Denise, Paoletti, Dollfus, Levillain, & Thibaut, 2010; O'Driscoll, & Callahan, 2008).

Sensory Gating

Sensory gating is a neurophysiological measure of attention and information processing observed during electroencephalographic (EEG) recording (Cadenhead, Light, Geyer, & Braff, 2000). Sensory gating is characterised by attenuation of the event-related potential (ERP) P50 by 9-73% upon repetition of an identical auditory stimulus in healthy controls (Cadenhead et al., 2000; Croft, Lee, Bertolot, & Gruzelier, 2001; Park, Lim, Kirk, & Waldie, 2015; Wan, Crawford, & Boutros, 2007). Sensory gating relates to the attenuation of redundant sensory information for the observer to maintain cognitive resources for processing important information (Mayer et al., 2012). Sensory gating ratios are higher (56-158%) in individuals with schizotypy compared to controls (Wan, Thomas, Pisipati, Jarvis & Bourtos, 2017). Deficits in sensory gating have been suggested to occur due to impairments in central inhibition in individuals with high levels of schizotypy (Cadenhead, et al., 2002). The resulting difficulty in inhibiting irrelevant stimuli, both internal and external at an early-preattentive stage of processing, is thought to explain the cognitive and attentional abnormalities of this population (Cadenhead et al., 2002; Evans, Gray, & Snowden, 2007; Venables, 1964).

While some studies have demonstrated deficits in sensory gating in people with high levels of schizotypy (Croft, Dimoska, Gonsalvez, & Clarke, 2004; Park, Lim, Kirk, & Waldie, 2015), further studies have indicated that sensory gating is specifically related to the disorganised (Evans et al., 2007; Park et al., 2015), the negative (Wang, Miyazato, Hokama, Hiramatsu, & Kondo, 2004), or the positive

(Croft, Lee, Bertolot, & Gruzelier, 2001) dimension of schizotypy. These disparate findings are likely to be due to methodological differences: some studies include smokers and others do not – A typical finding is that non-smoker low schizotypal participants have less of deficit in sensory gating than smoker high schizotypal participants (Wan, Crawford, & Boutros, 2006); Further, many of the studies use non-standardised questionnaire measures of schizotypy that do not have established psychometric properties (e.g., Croft et al., 2001); Other methodological differences include the inter-stimulus-interval (Louchart-de la Chapelle et al., 2005 and Wang et al., 2004, used unusually short ones that may cause the signals to interfere) or the intertrial interval (Croft et al., 2001 did not include randomisation allowing the brain to potentially prepare for stimulus onset). These differences highlight the importance of using valid, reliable, and theoretically-motivated methods.

To identify the cognitive basis of sensory gating, Jones, Hills, Dick, Jones, and Bright (2016) correlated sensory gating with participants' performance on a battery of tests of different types of inhibition based on an established taxonomy (Nigg, 2000), working memory, and intelligence. They identified a relationship between sensory gating and cognitive control measured through latent inhibition (Lubow & Kaplan, 1997). Latent inhibition is the increased response time associated with re-learning stimuli as relevant if they have been previously conditioned as irrelevant (Granger, Prados, & Young, 2012). It only occurs when the conditioning and test phase contexts are matched (Lubow, Rifkin, & Alek, 1976).

The relationship between sensory gating and latent inhibition led Jones et al. (2016) to theorise that sensory gating represents the identification of irrelevant stimuli during encoding due to previous experience and/or the ability to use top-down modulation to selectively attend only to relevant information. This is supported by findings that show attenuated latent inhibition in people with high schizotypy (Braunstein-Bercovitz, Rammsayer, Gibbons, & Lubow, 2002; Lubow, Kaplan, & De la Casa, 2001; but see Granger, Moran, Buckley, & Haselgrove, 2016). Inconsistent correlations between schizotypy and latent inhibition (Claridge, & Broks, 1984) might reflect a relationship that is limited to

specific positive dimensions of schizotypy (Gray, Fernandez, Williams, Ruddle, & Snowden, 2002; Lipp, Siddle, & Arnold, 1994). Indeed, Granger and colleagues (2016) found that latent inhibition correlates with the unusual experiences dimension (a positive symptom) of schizotypy which may relate to development of spurious associations leading to unusual thought patterns and delusions (Kapur, Mizrahi, & Li, 2005; Moran, Owen, Crookes, Al-Urzi, & Reveley, 2008). Similarly, Smith et al. (2013) indicate that impaired sensory gating is related to auditory and visual hallucinations in patients with schizophrenia, potentially due to compromised tempero-parietal circuitry (Ehlis et al., 2009; Vercammen, Knegtering, den Boer, Liemburg & Aleman, 2010). Such deficits have been linked to positive symptoms (Dinn, Harris, Aycicegi, Greene & Andover, 2002), specifically, auditory hallucinations (McGhie & Chapman, 1961; Oranje et al., 1999). This suggests a fundamental link between impaired temporo-parietal circuits, impaired attentional processes and sensory gating deficits in the production of positive symptomatology. If latent inhibition is related to the same underlying neurobiological markers as sensory gating, then we would expect the positive schizotypy and sensory gating to be correlated.

Smooth Pursuit Eye Movements

Smooth pursuit eye movement deficits have also been reliably found to correlate with schizotypy (Holahan & O'Driscoll, 2005; Lenzenweger & O'Driscoll, 2006; Smyrnis et al., 2007). During smooth pursuit eye movement tasks, participants must track a slowly moving target with their eyes (Bargary et al., 2017, Ettinger et al., 2015). Smooth pursuit eye movements rely on the ability to process sensory information about how a target is moving and use this information to activate and control fine motor movements (Levy, Sereno, Gooding & O'Driscoll, 2010; Siever & Davis, 2004; Thaker, 2008). Those with schizotypy typically show deficits in root mean square error, initial eye acceleration, and number of saccades, but not pursuit gain (Gooding, Miller, & Kwapil, 2000; Lencer, et al., 2015).

Smooth pursuit eye movements deficits are considered a reliable intermediate endophenotype for schizophrenia and schizoaffective disorders (Lencer, Trillenberg-Krecker, Schwinger, & Arolt, 2003;

Thaker, 2008; but see Hatzimanolis et al., 2015). Smooth pursuit eye movement deficits tend to be frontally mediated (Lencer et al., 2010). Negative and disorganised schizotypy is also associated with impairments in frontally-mediated neurocognitive processes (Cochrane, Petch & Pickering, 2012). The ability to correctly perceive and initiate movement has been linked to processes of communication (speech initiation and listening comprehension), cognition (Ettinger et al., 2015) and deficits in social interaction (Cohen, Mohr, Ettinger, Chan, & Park, 2015). These are negative dimensions of schizotypy and, therefore, we expect to establish a correlation between smooth pursuit eye movement accuracy and the negative dimension of schizotypy as predicted by Lee, Williams, Loughland, Davidson, and Gordon (2001) and Holahan and O'Driscoll (2005).

Prepulse Inhibition

Another reliable endophenotype of schizotypy is that of deficient prepulse inhibition: such deficiencies are apparent in patients with schizophrenia (Swerdlow et al., 2017), their unaffected relatives (Hasenkamp et al., 2010) and schizotypal individuals (Wan, Thomas, Pisipati, Jarvis & Bourtos, 2017). Pre-pulse inhibition is an operational measure of sensorimotor gating characterised by a reduction in the startle reflex when a weaker pre-stimulus precedes a subsequent strong stimulus (Graham, 1975). Prepulse inhibition reflects the ability to regulate sensory input at an early stage of attention processing, as it allows the filtering and inhibiting of irrelevant stimuli from entering higher cortical regions to prevent flooding of sensory information (Mena et al., 2016; Wan, Thomas, Pisipati, Jarvis & Boutros, 2017). Reduced prepulse inhibition may result in cognitive fragmentation and sensory overload, consistent with the symptoms observed in schizophrenia (Braff et al., 1978; Perry & Braff, 1994) and schizotypy (Giakoumaki, 2012).

Studies have found that impaired temporo-limbic circuitry is related to prepulse inhibition deficits, with the same circuits having also been linked to the occurrence of positive symptomatology in patients with schizophrenia (Javitt & Freedman, 2015). Indeed, prepulse inhibition deficits correlate more strongly with positive than negative symptomology (Braff, Swerdlow & Geyer, 1999). However,

Giakoumaki (2012) suggests that prepulse inhibition is more associated with negative or paranoid symptomology (see also Giakoumaki, Karagiannopoulou, Karamaouna, Zouraraki, & Bitsios, 2020). The data from Evans, Gray, and Snowden (2005) partially resolves the discrepant findings of Braff et al. and Giakoumaki et al.: in non-smoking participants, the relationship between positive schizotypy and prepulse inhibition holds, but for smokers, an alternative pattern emerges. Since, both sensory gating and prepulse inhibition are more strongly related to positive symptoms may also indicate a shared mechanism being involved in both endophenotypes and contributing to the manifestation of positive symptomatology. If these relations hold, then we would expect a correlation between positive symptomology and prepulse inhibition deficits.

Deviance Detection

Impaired deviance detection has also been identified as an additional neurophysiological endophenotype of schizophrenia. Deviance detection is typically measured using an auditory "oddball" paradigm wherein a sequence of repetitive stimuli is unexpectedly interrupted by a deviant stimulus (Fisher, Smith, Labelle & Knott, 2014; Leitman et al., 2010), causing an ERP called P300. The P300 ERP component represents the positive deflection occurring between 250ms and 500ms after a deviant stimulus onset (Earls, Curran & Mittal, 2016). Prolonged latency and reduced amplitudes of P300 to deviant stimuli has been replicated in those with schizophrenia and schizotypy (Bramon, Rabe-Hesketh, Sham, Murray & Frangou, 2005; Choi, Jang & Kim, 2014; Onitsuka, Oribe, Nakamura & Kanba, 2013).

The P300 response is thought to reflect activation of neural circuits within the temporal-parietal and medial-frontal cortex, associated with high-order cognitive functions, including working memory, goal-directed stimulus detection, and context updating (Takahashi et al., 2012). There is evidence of a relationship between reduced activation of these neural networks and reduced P300 amplitude, which in turn predicts increased reports of negative symptoms (Kim, Shim, Kim, Im & Lee, 2014). Contrastingly, studies have also demonstrated a significant relationship between deviance detection

and positive, but not negative, symptoms (Higashima et al., 2003). Therefore, it may be that mechanisms involved in deviance detection contribute to both positive and negative symptoms; or perhaps abnormal deviance detection is better at predicting one symptom type than the other.

The current study

Throughout this introduction, we have indicated what relationships we expect to find between endophenotypes and the symptom clusters of schizotypy. An additional empirical question addressed by the present study is whether the four endophenotypes that we have chosen to measure here overlap in their relationship with schizotypy. We have summarised evidence to suggest that there may be some overlap between these endophenotypes. There is evidence, however, that the brain regions responsible for sensory gating, smooth pursuit eye movement, prepulse inhibition, and deviance detection appear to overlap in schizotypal participants (Wan, Thomas, Pisipati, Jarvis, & Boutros, 2017). The present study, therefore, explored the relationship between four endophenotypes (sensory gating, smooth pursuit eye movements, prepulse inhibition, and deviance detection) of schizophrenia in order to understand whether these reflect the overall personality of schizotypy or whether they relate to clusters of symptoms. The exact nature and number of such clusters largely depends on sampling and the methods used to quantify schizotypal traits (Lin, Huang, Chang, Chen, Lin, Tsai, & Lane, 2013). We utilise the Schizotypal Personality Questionnaire (SPQ), as developed by Raine (1991). It is a self-report measure of schizotypal symptoms in a typical population. Of the many measure of schizotypy that exist, the SPQ has the highest reliability and is arguably the most widely used.

Method

Participants

An opportunity sample of 205 participants (130 female, 69 male, and 6 undisclosed, mean age=24.04 years, *SD*=7.88 years, range= 18 to 68 years; 158 were studying for an undergraduate or master's degree, 6 were studying for PhDs, the remainder did not have degrees) were recruited from Bournemouth from those who responded to an advert. We did not analyse the results by educational level as previous work has indicated no relationship between age, nor educational level and sensory gating (Lijffijt, Moeller, Boutros, Burroughs, Lane, Steinberg, & Swann, 2009). All participants had normal or corrected-to-normal hearing and vision. Participants were excluded if they self-reported any history of epilepsy, alcoholism, brain damage (including traumatic brain injury), psychoses, personality disorders, or were taking anti-psychotic medication. Participants were required to avoid consuming alcohol and nicotine (only 10% of participants smoked) 24 hours before the study: All confirmed that they had. This request may have introduced self-selection bias if only those who could cease smoking for this period participated. This research was approved by the Research Ethics committee of Bournemouth University and was carried out in accordance with the principles of the Declaration of Helsinki.

Design

A correlational design was employed in which sensory gating (measured as P50 attenuation, Sánchez-Morla, Santos, Aparicio, García-Jiménez, Soria, & Arango, 2013), latent inhibition (measured as difference in reaction time to respond to pre-exposed and not-pre-exposed stimuli, Lubow & Kaplan, 1997), smooth pursuit accuracy (measured as the root mean square error, RMSE, Bargary, Bosten, Goodbourn, Lawrance-Owen, Hogg, & Mollon, 2017; Kathman et al., 2014; Smyrnis et al., 2007), prepulse inhibition (measured as attenuation of the startle reflex measured as the difference in amplitudes of the ocular electrodes following the pre-pulse and pulse, Graham, 1975), and deviance detection (measured as P300 amplitude, Earls et al., 2017) were correlated with the subscales of the SPQ (Raine, 1991). Sensory gating and SPQ tasks were marked by two experimenters to increase inter-rater reliability (Potter, Summerfelt, Gold, & Buchanan, 2006): For sensory gating, two trained

experimenters identified the relevant peaks independently and then compared their answers; for SPQ, one experimenter counted the scores and the second verified this for accuracy. The inter-rater reliability for sensory gating was *r*=.93. Any disagreements or concerned were dealt with through discussion with the lab leader.

General Procedures and Materials

Participants underwent five tasks and one questionnaire sequentially in a random order usually over two days. This increased drop-outs, leading to unequal participant numbers across tasks as specified in the results. All were conducted in a quiet dedicated laboratory individually. Participants were instructed throughout by an experienced researcher.

Sensory Gating

Participants were fitted with an ActiCap electrode cap using a chinstrap. Participants were instructed to minimise any body, face, and eye movements. They were provided with an example of the auditory stimuli to be used in the experiment. Stimulus volume was first set at 75dB using an SPL meter for all participants but was reduced marginally if participants found this volume too uncomfortable. During recording, they were monitored for signs of drowsiness by monitoring the EEG for alpha waves. Participants were instructed to focus on a central black fixation cross on a white background throughout the experiment and to press the response pad whenever they heard a click. This task engaged the participants' attention. All participants had an accuracy of at least 90%.

Each trial consisted of a conditioning stimulus and a test stimulus, both of which were beeps: bursts of 4100Hz of approximately 10ms duration and an intensity of 70–75dB, delivered using speakers. There was an inter-stimulus interval (ISI) of 500ms. There was an inter-trial interval of between 9 and 10s to allow brain activity to return to baseline (Ettinger, Meyhöfer, Steffens, Wagner, & Koutsouleris,

2014). The experiment consisted of 135 paired-beep trials[2] with an additional 15 click trials (4 ms of the same frequency and volume) and was approximately 24 minutes long with two breaks.

EEG Recording and Analysis

ERPs were recorded via a 32-channel DC amplifier, using Brainvision Recorder and ActiCap software. Twenty-eight electrodes were mounted on a cap while four additional ocular electrodes were placed on the outer canthi and above and below one eye, which monitored horizontal (+HEOG, -HEOG) and vertical (+VEOG, -VEOG) eye movements respectively. Electrode impedances were kept under 10kΩ when possible but were accepted when below 20kΩ if the set-up time took longer than 40minutes[3]. The sampling acquisition rate was 2000Hz. FCz was the reference electrode during acquisition; the data were re-referenced to the average mastoids (TP9 and TP10) offline.

Using Brainvision Analyser, raw data were filtered using a 50Hz notch filter and a 10-40Hz band pass filter (24-dB/octave roll-off, Boutros, Korzyukov, Jansen, Feingold, & Bell, 2004). A 10Hz low filter has been shown to aid in differentiation between the P50 and N100 which can appear early at 50ms (Hazlett et al., 2015). Ocular corrections were made using a Gratton and Coles algorithm before semi-automatic data inspection was used to highlight and remove amplitudes exceeding -50/50µV or gradients exceeding 50µV/ms. For each participant, segmentations were made based on marker position for stimulus 1 (S1) and stimulus 2 (S2), which included 100ms prior to stimulus onset and up to 200ms post stimulus onset. Baseline corrections were carried out 100ms before stimulus onset. The analysis focused on the P50 ERP within a 40ms period between 40ms and 80ms post-stimulus onset for electrode Cz (Jones et al., 2016). P50 amplitude was obtained by calculating the difference between the P50 peak and the preceding negative trough (N40). N40 was identified as the most negative peak between 20ms and 50ms post stimulus onset. If no obvious S1 P50 was observed, the participant was removed (Gjini, Arfken, & Boutros, 2010); however, if no S2 P50 was observed then

[2] An average of 4% of trials were removed per participant due to noise in the data.
[3] This occurred in 22 cases. In these cases, the EEG signal was visually inspected prior to recording to assess data quality.

this was deemed to be full suppression and a value of 0.01μV was given. This technique was chosen since if a particular ERP could not be detected, taking a maximum value in the set time-frame may misrepresent the actual waveform. This procedure resulted in the removal of 9 participants.

To calculate sensory gating ratio for an individual, their average P50 amplitude for S2 was divided by the average amplitude for S1, then multiplied by 100 (S2/S1x100). In line with Jones et al. (2016), ratios of less than 100 were considered to represent sensory gating, with those of 100 indicating impaired sensory gating. Ratios higher than 150 were removed to prevent skew of the data from outliers (Gjini, Burroughs, & Boutros, 2011). A group-level sensory gating effect was observed, $t(88)=14.31$, $p<.001$, (see Figure 1 for the P50 distribution of S1 and S2, and for the P50 waveforms for S1 and S2). Figure 1 highlights that there were participants who demonstrated the sensory gating effect and those that did not, highlighting the individual variability in this effect.

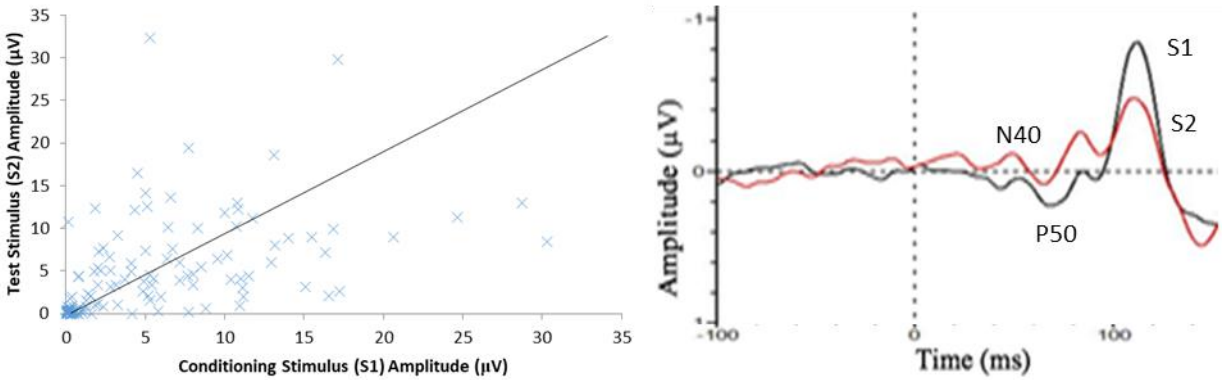

Figure 1. Left panel: P50 Amplitudes in response to first (S1) and second (S2) stimulus. The line at 45° is representative of the point where S1 and S2 amplitudes would be the same. The points below this line show an attenuation in P50 to the S2 following S1. Right panel: Grand average of the P50 waveforms taken from Cz (black line represents S1 and the ref/grey line represents S2).

Latent Inhibition

Stimuli consisted of five randomly connected straight black lines on a white background subtending 10° of visual angle. Four designs were created. These were presented in an array containing 20 identical stimuli (target-absent condition), or 19 identical and 1 unique (target-present condition), see Figure 2. Participants were instructed to identify whether there was a unique element within each array. The position of each stimulus was randomly generated in an imaginary 8 x 12 matrix. Participants were presented with 100 pre-exposure trials (50 target-present and 50 target-absent) in a random order. Only two of the stimuli were used in the pre-exposure phase (this was counterbalanced across participants). Stimuli remained on screen until the participant made a response. The test phase began immediately following the pre-exposure phase and participants were informed that they would be completing the same task, but the stimuli would change from trial to trial. The duration of this experimental session was approximately 8 minutes.

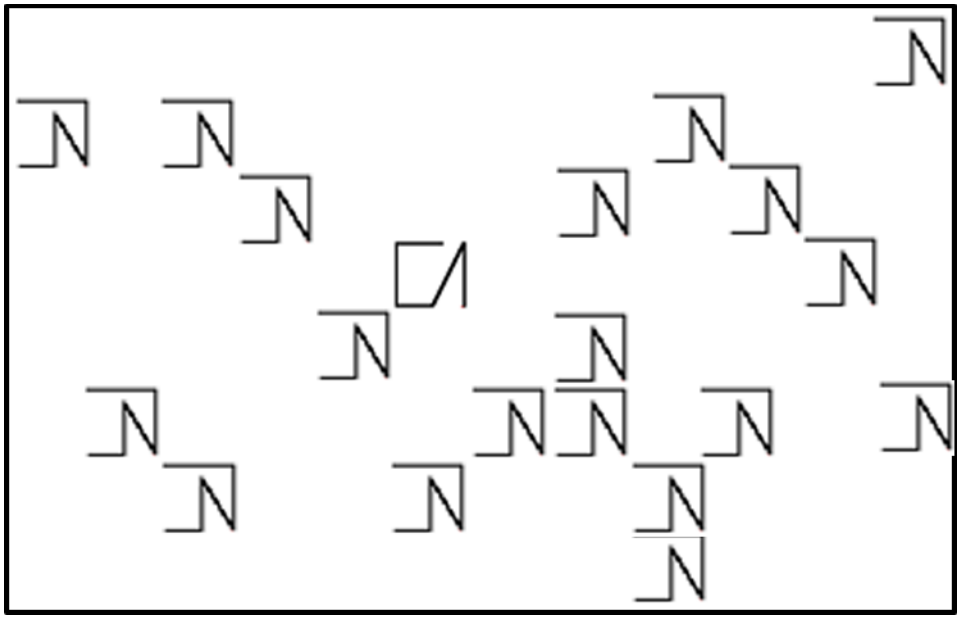

Figure 2. A Latent inhibition array for target present condition.

There were seven possible relationships between the distractors and targets from the pre-exposure phase to the test phase (as described in Lubow & Kaplan, 1997). However, only two are relevant to this study: 1) Target and distractor stimuli are the same in both phases (PE); 2) target and distractor

stimuli in the pre-exposure phase swap roles in the test phase (NPE). The average reaction time was recorded for each participant in each condition. During data pre-processing, we removed all latent inhibition effects that were -100ms or more negative since these values were greater than 1.96 SDs away from the mean. The effect of latent inhibition is measured by the reaction time difference in the PE condition (*M*=1892*ms*, *SE*=81) minus the NPE condition (*M*=1596*ms*, *SE*=71). This difference was significant, $t(162)=10.10$, $p<.001$, confirming the presence of the latent inhibition effect.

Smooth Pursuit Eye Movement Test

Participants were seated 72cm in front of a 22" Vision Master Pro510 computer screen running at 100Hz and were asked to place their chin on a chin rest, which was adjusted to fit (O'Driscoll, Lenzenweger & Holzman, 1998). Stimuli were displayed using a bespoke Experiment Builder (SR Research) programme running on a Windows 7 PC. An SR Research Eyelink CL 2008 was used to monitor eye movements of the participants' right eye. Eye-movements were calibrated and validated using the in-built nine-point on-screen procedure on the host computer, a Flatron L1510M. Participants were asked to track a 0.5° square that moved along a horizontal line in the middle of the screen for eight cycles, at a rate of 8 degrees per second. The stimuli moved within a visual angle of 20° for a duration of 20 seconds (O'Driscoll, et al., 1998). Data regarding the eye position was presented linearly (±12° visual angle). Eye movement data was digitalized (250Hz) and the average velocity of eye movement throughout the task was divided by the velocity of the moving stimulus to represent the level to which participants deviated from smooth pursuit (Ivleva et al., 2014). Any eye velocity three times or $1/8^{th}$ the speed of the target was excluded from the trial. To obtain a single number for each participant, we calculated the average RMSE (Smyrnis, 2008) of this position error value across all the valid trials (Avila et al., 2006). There was one outlier discovered during data preprocessing (1.96 SDs below the mean) and this was removed.

Prepulse Inhibition

Prepulse inhibition was measured using the attentional blink task undertaken during EEG recording using the same techniques as described for the sensory gating task. This task consisted of 144 trials, with each trial consisting of a weak and a louder startle-pulse overlaid to a white-noise background track of white noise presented at 75dB. The prepulse was presented 40% louder (76.5dB) and the pulse was presented at 90dB. Each pulse had an instantaneous rise time and lasting for 40ms. Prepulse onset was either 30, 60 or 120ms prior to pulse onset, randomised across trials. Participants were asked to focus on a black cross in the centre of the screen for the duration of the task. Between each prepulse-pulse trial, there was an intertrial interval of between 3 and 5s to allow brain activity to return to baseline. The task lasted approximately 6 minutes.

Data for the prepulse inhibition task was analysed using BrainVision Analyser 2.1. Filters were applied as described for the sensory gating task. Analysis was conducted on the ocular electrodes. For each participant, segmentations were made based on marker position for the prepulse and pulse including 100ms prior to stimulus onset and up to 200ms post stimulus onset. Baseline corrections were carried out 100ms before stimulus onset. Prepulse inhibition was obtained by calculating the magnitude of the blink reflex at the pulse.

Deviance Detection

The P300 ERP component was measured using the oddball paradigm. Participants were presented with 150 trials of which 135 were beeps (bursts of 4100Hz, 75dB at 10ms duration) and 15 were clicks (4ms duration at the same frequency and volume). There was an inter-trial interval of between 4 and 5s to allow brain activity to return to baseline. Participants were instructed to respond to the click sound.

Data were pre-processed in the same way as for the sensory gating task using BrainVision Analyser 2.1. Segmentation was based on the onset of the oddball stimuli. Baseline correction was applied using the 100ms immediately prior to the stimulus. The P300 component was identified as the largest

positive deflection between 250ms and 500ms (Boutros et al., 2004). P300 was calculated by subtracting the value of the negative trough immediately preceding the highest positive peak within that time frame. Much research reports P300 data at three midline sites (Fz, Cz, Pz) (Bramon et al., 2005); although several studies propose the Fz site as most appropriate for the endophenotype (Tsai et al., 2003; Gallinat et al., 2003). Thus, the present study measured P300 amplitude and latency to the deviant stimulus from electrode Fz. Any P300 amplitude above 30 μV was removed as it was considered an implausible value based on the typical size of ERPs.

Schizotypal Personality Questionnaire

Participant's schizotypy level was measured using the SPQ (Raine, 1991). It has 74 items that contribute to nine subscales exploring the DSM criteria (APA, 1994): see Table 1. Each question is answered true or false. In Raine's (1991) original research, the SPQ was found to have high internal reliability, sampling validity, convergent validity, test-retest reliability, discriminant validity and criterion validity. Subsequent research has similarly concluded that the SPQ is a valid and reliable instrument for measuring schizotypal characteristics in the general population (Şener, Bora, Tekin, & Özaşkınlı, 2006; Takahashi, et al., 2010). The SPQ has also been previously used in research into schizotypy traits and deficits in eye tracking (Takahashi, et al., 2010; Vettise, 2012).

The nine subscales of the SPQ can be clustered into three dimensions in line with the symptom clusters of schizophrenia according to the DSM-IV (American Psychiatric Association, 1994): cognitive-perceptual (positive); interpersonal (negative); and disorganised (Wuthrich & Bates, 2006). Confirmatory factor analyses on the SPQ indicate a fourth dimension – paranoid (Compton, Goulding, Bakeman, & McClure-Tone, 2009). To select which model to use in our data, we ran a confirmatory factor analysis with 3 or 4 dimensions, and an exploratory factor analysis. The resulting scree plot indicated that only two resulting factors had Eigenvalues above one. A third factor had an Eigenvalue of 0.93. The fourth factor had an Eigenvalue of 0.63. The difference in cumulative explained variance between the 3 (72.61%) and 4 (79.12%) factor model was only 6.51%. Our three-factor model matched

that of Raine (1993). We, therefore, interpret this as providing supporting evidence for a three-factor model of the SPQ, which is largely similar to the three factors in the Multidimensional Schizotypy Scale (Kwapil, et al., 2018).

Results

The mean score on the SPQ was 32.22 (*SD*=21.81, see Table 1). This was comparable to other published studies using this questionnaire, though on the high side: *M*=26.9, *SD*=11.0 (Raine, 1991); *M*=27.34, *SD*=12.41 (Smyrnis et al., 2007); *M*=30.00, *SD*=9.68 (Wuthrich, & Bates, 2006). We ran two separate analysis protocols. Firstly, we ran correlations summarised in Table 2: We used a hierarchical approach to this analysis, first correlating each neurophysiological test with SPQ overall, before each factor in the three-factor model. To establish if an endophenotype was related more to one factor of SPQ than others, we compared the correlation coefficients using Fisher's *r* to *z* test available at https://www.psychometrica.de/correlation.html. Finally, we correlated these measures with each individual subscale of the SPQ. Following the first step, we applied the appropriate correction to the alpha level (Bonferroni – α=.017 – at step two and Bonferroni-Šidák – α=.006 – for step three). The choice of correction was used based on the number of comparisons to be made: the Bonferroni correction is highly conservative and useful for when there is potential for increased inflation of the alpha level. When conducting more than six post hoc tests, the Bonferroni test becomes too conservative and risks Type II errors; therefore we applied the Bonferroni-Šidák comparison (Field, 2010). For comparisons across correlations, we used α=.10 due to the lack of power in this analysis to avoid making Type II Errors. All analyses were conducted using SPSS version 26.

Table 1.
Mean (and standard deviation), range, and measures of normality of distribution (skewness and Kurtosis) of the SPQ and its subscales.

Measure	Mean (SD)	Range	Skewness	Kurtosis
SPQ Total	32.22 (18.71)	4 to 72	.387	-1.12
Positive	6.59 (5.41)	0 to 16	.308	-1.43

Negative	10.90 (6.83)	0 to 24	.233	-1.09
Disorganised	6.48 (6.48)	0 to 16	.302	-1.01

Sensory gating was found to be significantly related to schizotypy, $r(83)=.38$, $p<.001$, and all its factors, as shown in Figure 3. The correlation coefficients did not differ significantly across the dimensions largest, $z=1.11$, smallest $p=.133$. A contrasting pattern was found with latent inhibition: it was not significantly related to schizotypy, $r(100)=-.14$, $p=.102$, nor any clusters, shown in Figure 4. There were no differences in magnitudes of the correlations across the factors, largest $z=0.42$, smallest $p=.335$. A mediational analysis between sensory gating, latent inhibition and schizotypy was not run because sensory gating did not significantly correlate with latent inhibition, $r(58)=-.07$, $p=.585$. To highlight that sensory gating and latent inhibition were unrelated to each other, we compared the correlation coefficients for each factor using Fisher's *r* to *z* test. The relationship between sensory gating and the dimensions of schizotypy was different to the relationship between latent inhibition and the dimensions of schizotypy: positive dimension, $z=4.28$, $p<.001$; negative dimension, $z=2.66$, $p=.004$; and disorganised dimension, $z=3.06$, $p<.001$,

Deficits in smooth pursuit eye movements correlated with schizotypy, $r(181)=.15$, $p=.042$, specifically the negative and disorganised dimensions (see Figure 5). However, there were no differences in magnitudes of the correlations across the factors, largest $z=0.77$, smallest $p=.220$. Figure 6 shows the lack of relationship between prepulse inhibition and schizotypy in this study, $r(34)=.11$, $p=.516$. There were no differences in magnitudes of the correlations across the factors, largest $z=0.90$, smallest $p=.180$. Finally, deviance detection, as measured by P300, correlated with schizotypy, $r(68)=.24$, $p=.04$. There were no differences in magnitudes of the correlations across the factors, largest $z=0.52$, smallest $p=.301$(see Figure 7).

Table 1.

*Correlations between subscales of SPQ and sensory gating (*N=*85), latent inhibition (*N=*146), smooth pursuit eye movement* RMSE *(*N=*183), prepulse inhibition (μ*V, N=*36), and P300 (μ*V, N=*77).*

SPQ Dimensions & Item	Sensory Gating	Latent Inhibition	Smooth Pursuit Eye movement	Prepulse Inhibition	Deviance Detection
Positive Dimension	**.44***	**-.12**	**.09**	**.16**	**.22**
Ideas of Reference	.31*	-.17*	.07	.26	.07
Odd Beliefs/Magical Thinking	.39*	-.08	.07	.14	.24
Unusual Perceptual Experiences	.43*	-.14	.10	.15	.18
Suspiciousness[+]	.07	-.15	.12	-.01	.00
Negative Dimension	**.29***	**-.07**	**.17***	**-.06**	**.22**
Excessive Social Anxiety	.07	.01	.19*	-.01	.03
Constricted Affect	.34*	-.06	.11	.01	.19
No Close Friends	.30*	-.11	.12	-.16	.32*
Disorganised Dimension	**.37***	**-.11**	**.15***	**.00**	**.30***
Odd or Eccentric Behaviour	.39*	-.15	.15	.03	.25*
Odd Speech	.28*	-.05	.11	-.04	.32*
Total SPQ	**.38***	**-.14**	**.15***	**.11**	**.24***

Note: + Also contributes to the negative dimension, * Significant after alpha level correction

Finally, we ran correlations between the endophenotypes and found that they were largely unrelated: There were no significant correlations, largest r=.14, smallest p=.322 (for sensory gating and smooth pursuit eye movement errors, consistent with Ivleva et al., 2014). Using Fisher's r to z test, we found that the positive dimension was related to sensory gating more so than to SPEM, z=2.87, p=.002, prepulse inhibition, z=1.51, p=.066, and deviance detection, z=1.55, p=.061. The negative dimension was more related to sensory gating, z=1.74, p=.014, and deviance detection, z=1.35, p=.088, than to prepulse inhibition. The disorganised dimension was more related to sensory gating than to SPEM, z=1.78, p=.037, and prepulse inhibition, z=1.88, p=.03. The disorganised dimension was also more related to deviance detection, than to prepulse inhibition, z=1.48, p=.030. These results suggest that symptomology relating to each endophenotype are part of a heterogeneous set of symptoms with limited overlap.

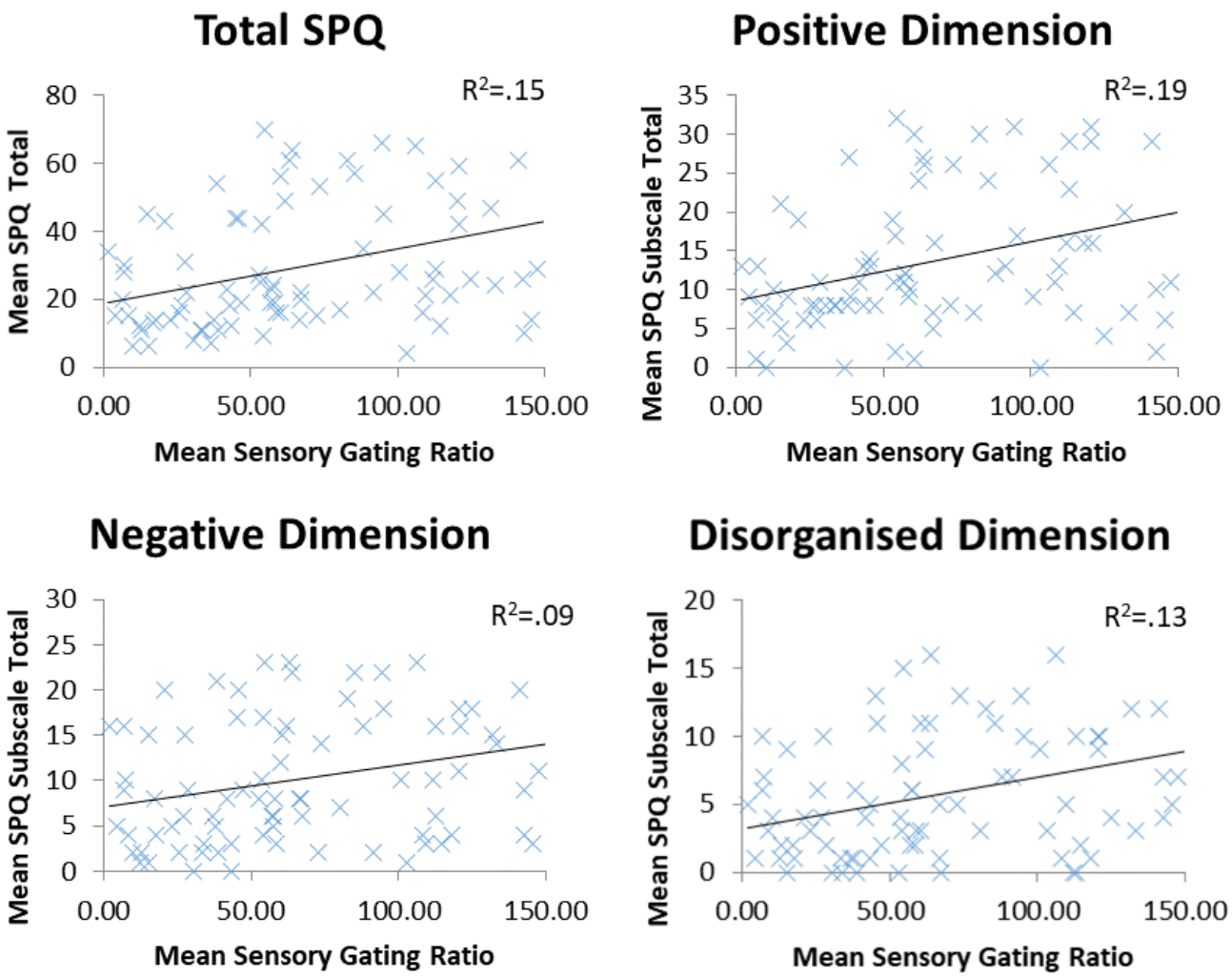

Figure 3. Correlations between schizotypy (left panel: total; right panel: positive, negative, and disorganised dimensions) and sensory gating ratio. Significant relationships are indicated with a line of best fit.

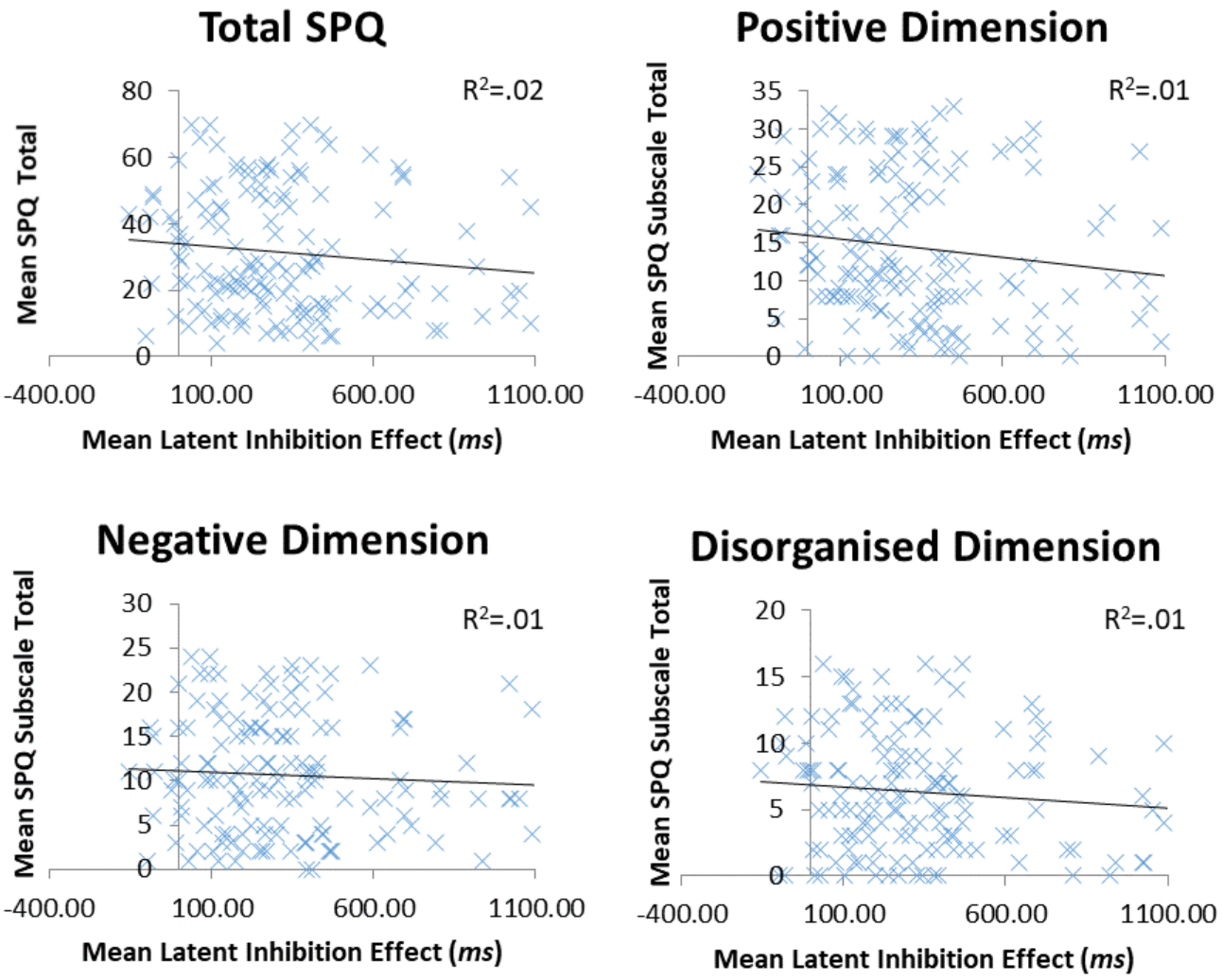

Figure 4. Correlations between schizotypy (left panel: total; right panel: positive, negative, and disorganised dimensions) and latent inhibition. Significant relationships are indicated with a line of best fit.

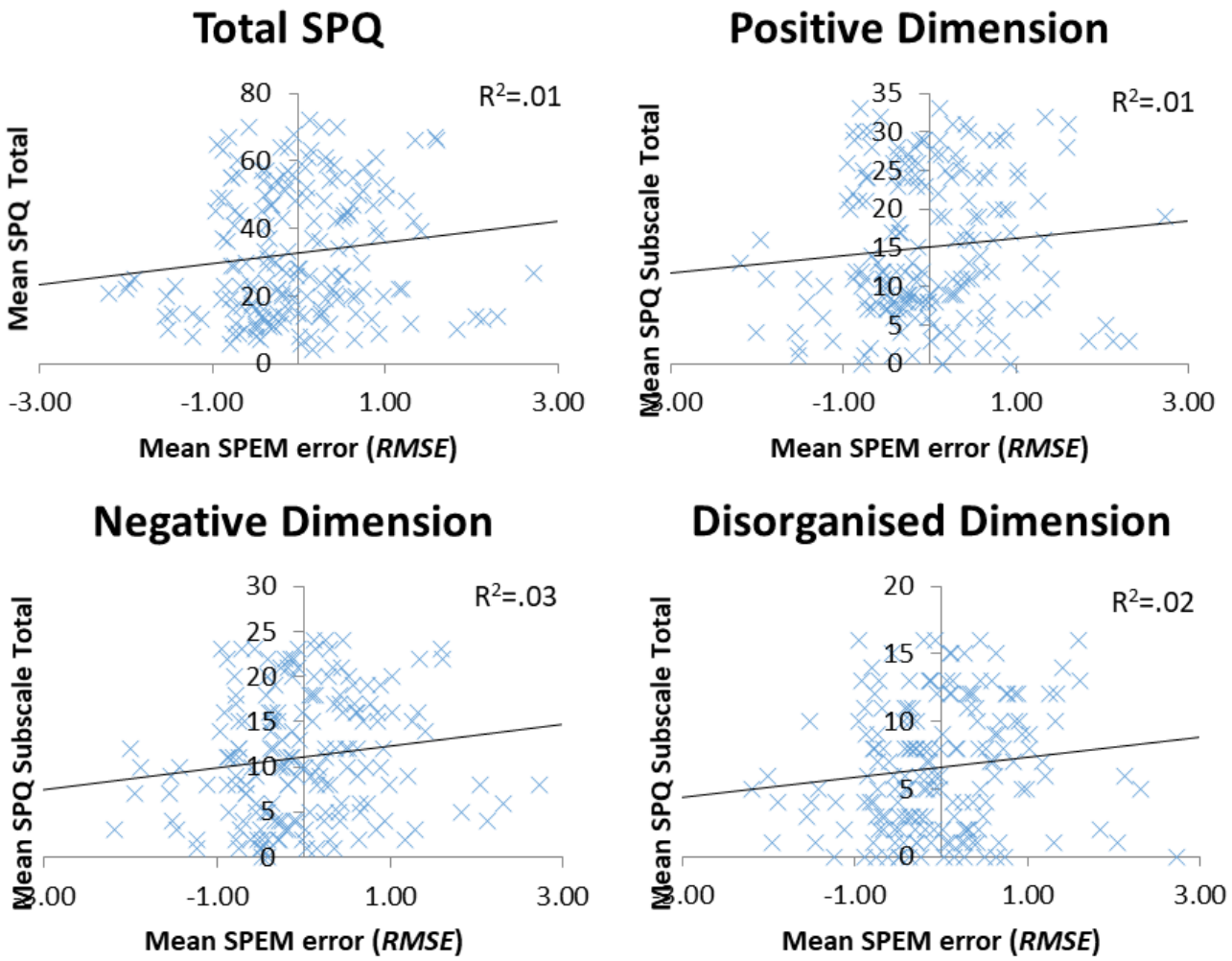

Figure 5. Correlations between schizotypy (left panel: total; right panel: positive, negative, and disorganised dimensions) and smooth pursuit error. Significant relationships are indicated with a line of best fit.

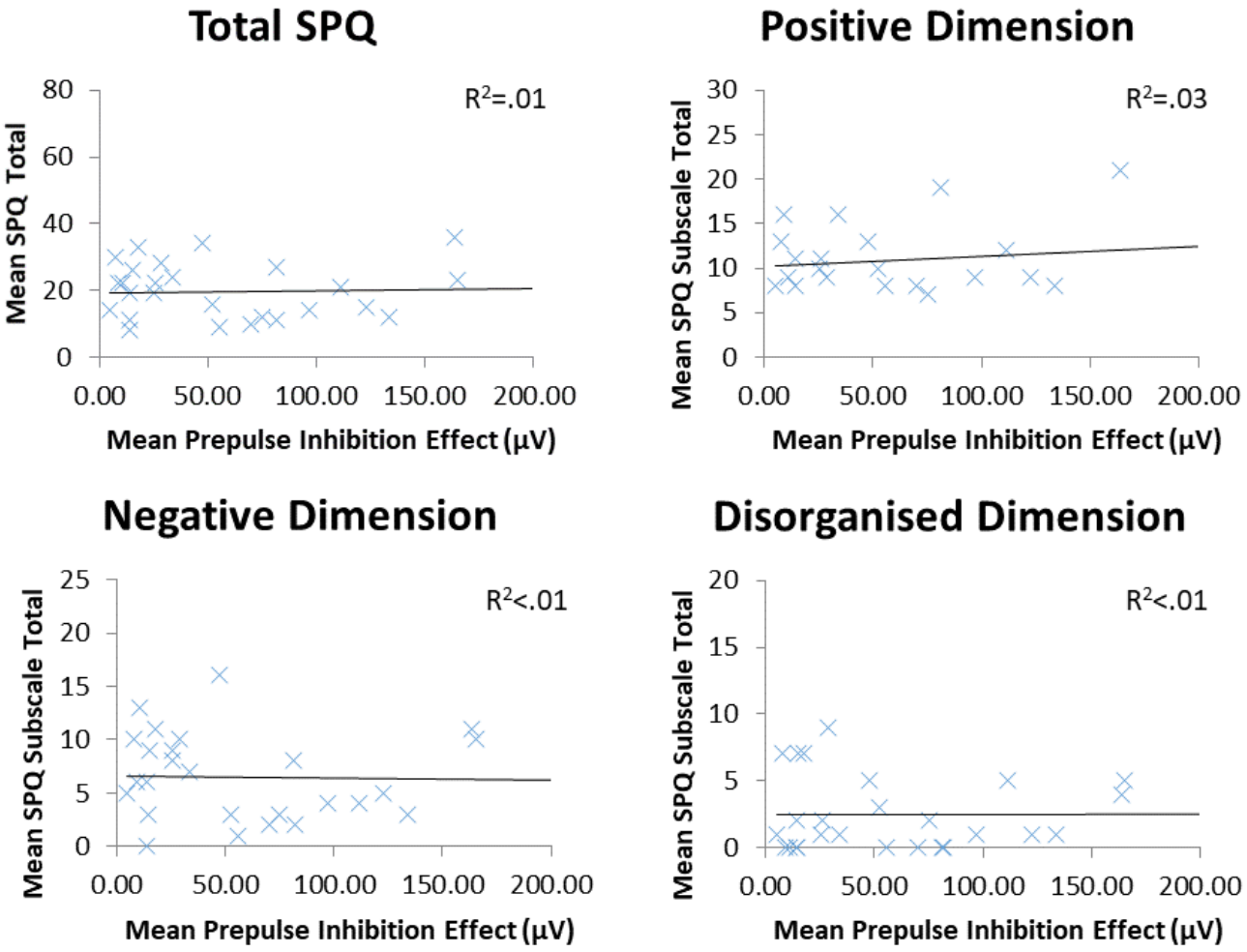

Figure 6. Correlations between schizotypy (left panel: total; right panel: positive, negative, and disorganised dimensions) and prepulse inhibition. Significant relationships are indicated with a line of best fit.

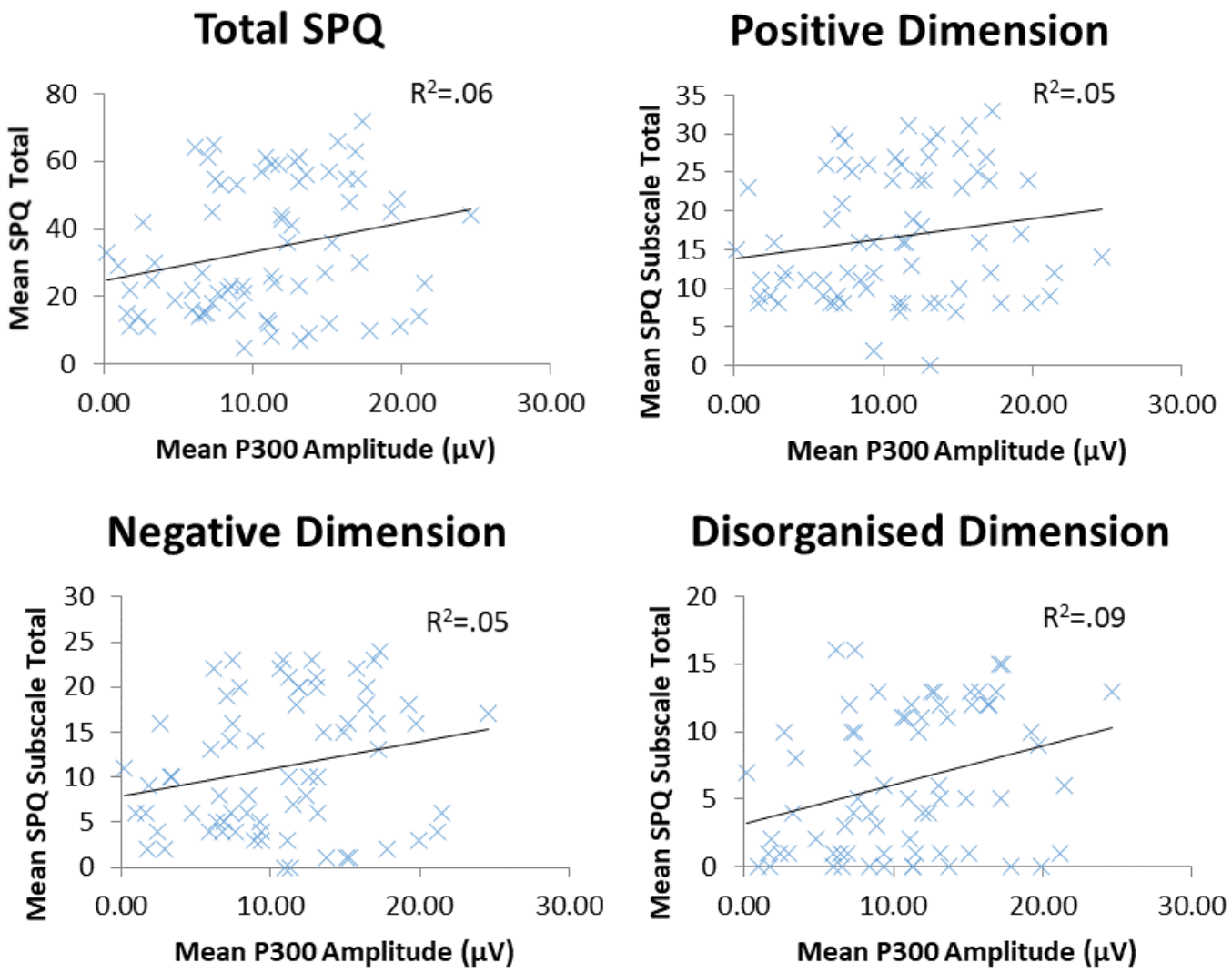

Figure 7. Correlations between schizotypy (left panel: total; right panel: positive, negative, and disorganised dimensions) and P300 amplitude. Significant relationships are indicated with a line of best fit.

To directly answer how the endophenotypes are related to SPQ, we used multidimensional scaling (Cox & Cox, 2008; Gower, 1966). This was used to reduce the complexity of the data and to map the dependent variables based on their similarity in abstract 2-D Cartesian space. This technique preserves the original distance between variables as well as possible. As such, variables similar to one another will tend to cluster more closely to each other in Cartesian space. The analysis was done in R v.3.6.2

(R Core Team, 2019) using the "ggpubr" v.0.2.4 package (Kassambara, 2019). Prior to analysis, all measures were centred with a mean of 0. The dependent variables were then separated into three clusters using Hartigan and Wong's (1979) *k*-means clustering method. This is an iterative algorithm that partitions the data into *k* clusters by minimising the sum of squares between data points and the centre of their assigned cluster.

The results are presented in Figure 8[4]. The SPEM task formed a cluster with two of the SPQ subscales: Excessive Anxiety, and Suspiciousness. The Sensory Gating task, on the other hand, formed a cluster with the remaining seven SPQ subscales: Odd Beliefs, Constricted Affect, Unusual Perception, Odd Behaviour, Ideas of Reference, No Close Friends, and Odd Speech. Finally, Latent Inhibition formed a third cluster with Deviance Detection. Thus, while showing some similarity to each other, Latent Inhibition and Deviance Detection were distinct from the SPQ subscales.

[4] Pre-pulse inhibition was not included in the multidimensional scaling analysis due to the small number of observations. However, when included, it formed a cluster consisting only of itself and was distinct from the remaining measures.

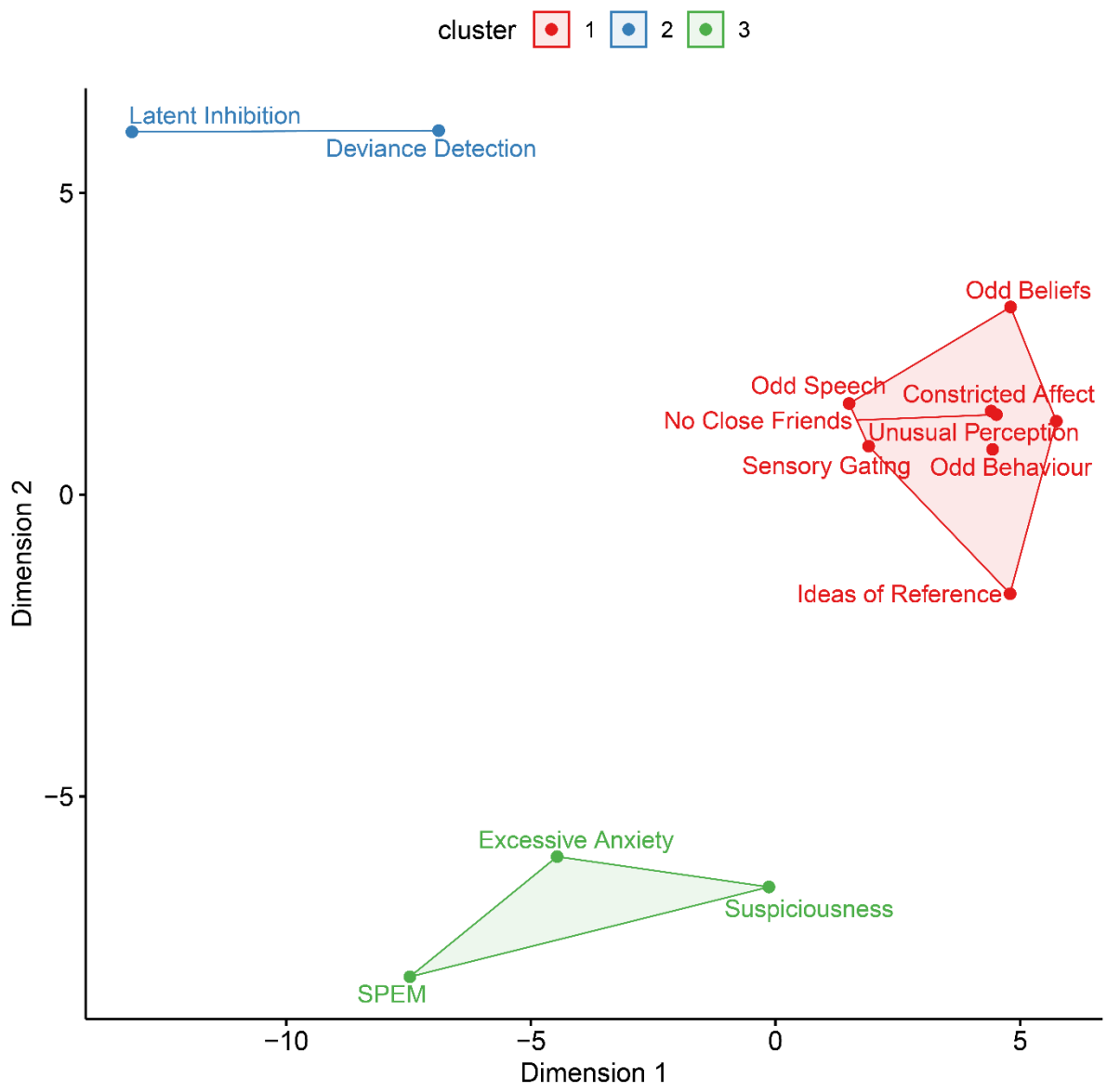

Figure 8. Results from multidimensional scaling of latent inhibition, deviance detection, sensory gating, SPEM, and the 9 subscales of the SPQ. The variables were partitioned into 3 clusters using the k-means method. *Note*: pre-pulse inhibition was not included due to the small number of observations.

Discussion

We attempted to explore four endophenotypes of schizotypy, latent inhibition, and how they relate to different clusters of symptoms. We explored sensory gating, thought to represent pre-conscious

attention and information processing (Cadenhead et al., 2000), smooth pursuit eye movements, thought to measure visual motion processing, attention, working memory, and oculomotor inhibition (the ability to inhibit eye movements, Siever & Davis, 2004), prepulse inhibition, thought to measure the filtering of sensory information (Wan et al., 2017) and deviance detection, thought to measure working memory, goal-directed stimulus detection, and context updating (Takahashi et al., 2012). We found differing patterns of correlations among the different endophenotypes and no correlations between the endophenotypes themselves, indicating they represent the action of different gene clusters causing different presentations of behaviour.

Sensory gating was found to correlate with all symptom clusters, but most strongly with the positive dimension representing unusual perceptual experiences, ideas of reference, and odd beliefs. Indeed, the positive dimension of schizotypy correlated significantly more strongly with sensory gating than any of the other endophenotypes. Given that sensory gating is the brain's way of limiting the perceptual input by attenuating repeated sounds, it is no wonder that there would be a correlation between sensory gating and unusual perceptual experiences. Utilising conjecture, we can explain how sensory gating might be related to the presentation of the personality. Here, we propose that the inability to inhibit repeated sounds (i.e., sensory gating deficits) causes unwanted percepts to interfere with cognition. The extra sensory input (the uninhibited repeated sounds) causes those with sensory gating deficits to unconsciously (given that sensory gating is pre-attentive, Cheng, Chan, Niddam, Tsai, Hsu, & Liu, 2016) process more sounds than other people. While it is impossible to predict the impact of additional sensory input on cognitive function, reasoning from other domains where unusual perceptual input leads to paranoid delusions (such as in Capgras Delusion, whereby patients believe known individuals are replaced by imposters due to a disconnect of unconscious face recognition, Ellis, Lewis, Moselhy, & Young, 2000). Therefore, it is possible that the additional sensory input leads to odd beliefs. Though not observed in our sample, it could also lead to other positive symptoms such as ideas of reference and suspiciousness in more clinical populations. Indeed, schizotypal odd beliefs have been shown to predict belief in conspiracy theories (Barron, Morgan, Towell, Altemeyer, & Swami,

2014; Darwin, Neave, & Holmes, 2011). We are aware that this argument goes well beyond what the present data can show. However, one of the key areas of future research is how endophenotypes and basic neurophysiological functions relate to the cause and consequence of symptoms.

In our study, smooth pursuit eye movement errors related primarily with negative and disorganised symptoms of schizotypy. Notably, there was no overlap with symptoms identified to be related to sensory gating and the two endophenotypes did not correlate with each other. Ettinger et al (2015) suggested that smooth pursuit eye movement deficits might affect communication and cognition. Deficits in communication are likely to lead to social interaction problems. In this study, we did not find a link between smooth pursuit deficits and odd speech nor no close friends (subscales of the SPQ) as we would have predicted. However, we did find relationships between smooth pursuit deficits and odd behaviour and excessive social anxiety. This suggests that the mechanism by which smooth pursuit eye movement deficits affect those with schizotypy is not as simple as odd eye movements affecting communication skills as we had surmised. Instead, there are more subtle issues associated how the world is interpreted leading to social anxiety and constricted affect. Further, our MDS analysis suggested that smooth pursuit eye movement deficits could also be related to suspiciousness, which also contributes to the negative dimensions of schizotypy and may be related to the excessive social anxiety trait given the links between anxiety and suspiciousness (Hubert & Smith, 2005). One caveat with the preceding argument must be noted regarding the selection of participants in our study: we did not exclude those with affective or anxiety disorders and this may have enhanced the scores on the negative dimension of schizotypy. However, the presence of affective and anxiety disorders in the community is approximately 17% (Mind, 2021), so any limitation in our sample should only add noise to the data rather than invalidate our findings.

In this study, we failed to find the predicted relationship between prepulse inhibition and any aspect of schizotypal personality. These results are in contrast with Giakoumaki (2012) and Giakoumaki et al (2020) who found correlations with negative dimensions of schizotypy and Braff et al (1999) and Evans

et al (2005) who found correlations with positive dimensions. Abel, Jolley, Hemsley, and Geyer (2004) highlight that in non-clinical groups the relationship between prepulse inhibition and schizotypal traits is not consistent, especially when compared to clinical groups. Our data may, therefore, reflect this inconsistency. While not significant, the correlation coefficients between the positive dimension of schizotypy and prepulse inhibition were larger and approaching significance compared to the negative dimensions and were similar in magnitude (r=.16) to those reported by Evans et al (2005) for the same onset times (r=.25 to r=35).

Our final tested endophenotype was deviance detection as measured by P300 from an oddball paradigm. We found that the P300 correlated with all dimensions of schizotypy. Our results are therefore consistent with those of Kim et al. (2014) and Higashima et al. (2003). These results suggest that deficits in detecting deviance or odd stimuli and the associated impaired fronto-temporo-parietal circuitry and working memory affect the entire range of observed symptoms. Using conjecture, it is possible to theorise as to why the inability to detect odd stimuli might lead to odd behaviours.

The MDS analysis was broadly consistent with this analysis: it suggested that sensory gating was clustered with most of the symptoms of schizotypy, including the disorganised dimension, except two of the negative subscales (excessive anxiety and suspiciousness). Given the MDS analysis was the most reliable of our analyses (based on the need for corrected comparisons), we accept that notion that sensory gating is broadly related to most of the subscales of schizotypy. These results are mostly consistent with Croft et al. (2001), but also show clear similarities with Evans et al. (2007) if one takes the MDS analysis at face value. However, because it is less related to two negative dimensions, in less powerful experiments, there is potential for this correlation not to be revealed. Our results offer potential to explain the rather disparate findings in terms of what schizotypy is related to: Because of the unreliability of the correlations between the disorganised dimension and half of the negative symptoms with schizotypy, these correlations may not always be found.

In this study, we also sought to explore how sensory gating might be linked to symptoms through its most significant cognitive predictor, latent inhibition (Jones et al., 2016). Our results did not provide evidence supporting our predictions for two reasons: 1. we did not find a significant correlation between latent inhibition and sensory gating; and 2. latent inhibition was not associated with any subscales of schizotypy in our MDS analysis. This novel finding suggests that the link between sensory gating and observed symptomology was not, as we had expected, directly through latent inhibition.

We believe that there are several possible reasons why latent inhibition was not found to correlate with sensory gating in the current work. As the same equipment and experimental methods were used in the current study as in Jones et al. (2016), inconsistencies were not due to methodological differences (Boutros, Korzyukov, Jansen, Feingold, & Bell, 2004; Granger et al., 2016). Indeed, the present study had ten times as many participants for exploring this correlation than Jones et al.'s. The analytical differences (where in addition to a bivariate correlation between sensory gating and latent inhibition, Jones et al. also ran a correlation partialling out intelligence and working memory) between the studies also fail to account for the discrepancies in the findings. Therefore, the differences may lie in individual differences in the participants or that the initial correlation was a spurious one. There may be some participants for whom latent inhibition is related to sensory gating. This suggests that individual differences in the expression and consequence of sensory gating might explain the lack of correlation. Alternatively, this was a Type 1 error in the previous work and the results from the larger sample are more reliable.

The notion that there are individual differences in the way people express a neurobiological marker should not come as a surprise. An individual's neurodevelopment will be influenced by many environmental factors (Murray, O'Callaghan, Castle, & Lewis, 1992). Different presentations of schizotypy and schizophrenia may reflect either the action of different genes or different environmental influences. Indeed, developmental studies have indicated that, while a common latent (potentially genetic) influence explains much of the heritability of schizotypy, there are distinct effects

of alternate (genetic) factors on certain symptom clusters (Ericson et al., 2011; Lin, Su, Kuo, Hsiao, Soong, & Chen, 2007) that may lead to differential effects of symptomology on cognitive performance (Sahakyan, & Kwapil, 2016). Smyrnis, Avramopoulos, Evdokimidis, Stefanis, Tsekou, and Stefanis (2007) have highlighted that negative symptoms of schizotypy are more strongly related to a particular gene (COMT) than positive and disorganised symptoms. Furthermore, the conclusions from large-scale biomarker studies indicate the wide variety of outcomes may reflect misdiagnoses or erroneous categorisation of disorders (Tamminga, Pearlson, Keshavan, Sweeney, Clementz, & Thaker, 2014). Several genetic studies have failed to find associations with particular genes and schizotypy (Hatzimanolis, et al., 2015; Stefanis, et al., 2007). The different environmental interactions change the way genetic predispositions manifest themselves, as has been noted in schizophrenia (Harrison & Owen, 2003) and schizotypy. When testing adults, people have many years of coping with having a maladaptive gene before symptoms present themselves. People whose alpha-7 nicotinic receptor gene (Gene 15q14), the gene thought to be responsible for sensory gating (Raux, et al., 2002), acts differently to the typical population, may employ different cognitive strategies to cope with the consequences of the maladaptive gene. Different coping strategies may even alter brain structure (Pantelis et al., 2005). Given that symptoms associated with schizotypy and schizophrenia are not usually detected until teenage years, this line of reasoning suggests different outcomes from the same cause. Further, it highlights how development can lead to differential effects of psychotropic medication despite apparently similar underlying causes (Jajodia et al., 2015).

The consequence of the preceding premise is that to fully understand symptomology and outcomes, one must fully explore the development of a neurobiological disorder. The relationship between genes and endophenotypes has been explored. The link between endophenotypes and cognition have been investigated by several authors (Cadenhead et al., 2002; Levy et al., 2010). However, few studies then attempt to link these with symptoms. It is difficult to see how specific endophenotypes (e.g., deficits in smooth pursuit eye movements) could relate to the expressed symptomology of disorders such as schizophrenia. Potentially, there may be multiple causes of an abnormal behaviour and taking a snap-

shot of such behaviour in adulthood masks how the behaviour was learnt. It may be that there is some common cause to symptomology and an endophenotype or it may be that the endophenotype (usually more fundamental biologically) is causing the symptomology through an, as yet, unknown mechanism. In this discussion, we have made some highly speculative suggestions of how they might link. However, to fully understand the link between endophenotypes, cognition, behaviour, and symptoms a large-scale longitudinal study is warranted. A similar point has been made following the results of the Bipolar and Schizophrenia Network for Intermediate Phenotypes studies indicating that it is important to establish the pathway from endophenotype to psychosis (Tamminga, Pearlson, Keshavan, Sweeney, Clementz, & Thaker, 2014). Indeed, Gagné, Hérbert, and Maziade (2015) have indicated that atypical early visual processing (influenced by genes or the environment) might be responsible for later schizotypal development.

The present results add to the burgeoning literature of schizotypy and its endophenotypes. We have shown that sensory gating, smooth pursuit eye movement deficits, and deviance detection, while all potential predictors of schizotypy, predict different clusters of symptoms. Sensory gating deficits are related to positive symptoms of schizotypy that may be the result of additional sensory input, and this was unrelated to smooth pursuit eye movement deficits.

Acknowledgements

The authors would like to thank Matt Green for technical assistance in the set-up of the eye-trackers and EEG equipment. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. This work was conducted between 2015-2016 and between 2019-2020.

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