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Cortical Suppression to Delayed Self-Initiated Auditory Stimuli in Schizotypy: Neurophysiological Evidence for a Continuum of Psychosis

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Abstract

Schizophrenia patients have been shown to exhibit subnormal levels of electrophysiological suppression to self-initiated, button press elicited sounds. These self-suppression deficits have been shown to improve following the imposition of a subsecond delay between the button press and the evoked sound. The current study aimed to investigate whether nonclinical individuals who scored highly on the personality dimension of schizotypy would exhibit similar patterns of self-suppression abnormalities to those exhibited in schizophrenia. Thirty-nine nonclinical individuals scoring above the median (High Schizotypy) and 41 individuals scoring below the median (Low Schizotypy) on the Schizotypal Personality Questionnaire (SPQ) underwent electroencephalographic recording. The amplitude of the N1-component was calculated while participants (1) listened to tones initiated by a willed button press and played back with varying delay periods between the button press and the tone (Active conditions) and (2) passively listened to a series of tones (Listen condition). N1-suppression was calculated by subtracting the amplitude of the N1-component of the auditory evoked potential in the Active condition from that of the Listen condition, while controlling for the activity evoked by the button press per se. The Low Schizotypy group exhibited significantly higher levels of N1-suppression to undelayed tones compared to the High Schizotypy group. Furthermore, while N1-suppression was found to decrease linearly with increasing delays between the button press and the tone in the Low Schizotypy group, this was not the case in the High Schizotypy group. The findings of this study suggest that nonclinical, highly schizotypal individuals exhibit subnormal levels of N1-suppression to undelayed self-initiated tones and an abnormal pattern of N1-suppression to delayed self-initiated tones. To the extent that these results are similar to those previously reported in patients with schizophrenia, these findings provide support for the existence of a neurophysiological "continuum of psychosis".

Keywords

schizophrenia, EEG, N1-suppression, schizotypy, continuum of psychosis

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Many psychotic symptoms, such as the passivity experiences, have been argued to emerge because of an inability to suppress the sensory consequences of self-generated actions leading to an inability to differentiate between self-generated and externally generated events.[1,2] Evidence for this idea lies in the finding that, in marked contrast to psychologically healthy participants, schizophrenia patients with psychotic symptoms can tickle themselves.[3] During self-generated actions, neural signals known as corollary discharges are sent to sensory areas to suppress cortical responsiveness to the resulting sensation, which enables a distinction to be made between sensations that are self-generated and sensations generated by the external environment.[4] These corollary discharges are believed to be deficient in patients with schizophrenia, leading to abnormal predictions to self-generated actions and subsequently misattributions of agency.[1,2]

Psychophysiological evidence of corollary discharge function has been provided by electroencephalographic (EEG) studies of self-generated auditory stimuli. These studies have typically found that the amplitude of the N1-component of the auditory-evoked potential (a volume-dependent component,[5] believed to be generated in the primary auditory cortex) is reduced (suppressed) in healthy participants when listening to self-initiated auditory stimuli (eg, during talking) compared

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with when passively listening to identical auditory stimuli that are externally generated.[6,7] However, schizophrenia patients have consistently been found to exhibit subnormal levels of N1-suppression during talking.[8-10] Furthermore, positron emission tomography studies have shown that when healthy individuals produce words, activity in the frontal cortex increases, along with a concomitant decrease in temporal cortex activity.[11] In patients with schizophrenia who are experiencing auditory verbal hallucinations, temporal lobe structures are activated instead of being suppressed.[12] This disrupted connectivity between the two brain areas has been suggested to reflect corollary discharges from speech areas in the frontal lobes failing to inform the temporal lobes of the impending onset of self-generated speech, or even potentially inner speech.[13] Support for this contention is provided by a single photon emission tomography study which showed that Broca's area, a key site of speech initiation, was abnormally active in schizophrenia patients who were experiencing auditory verbal hallucinations.[14] This finding is consistent with the suggestion that auditory hallucinations ultimately arise from inner speech being misperceived as an externally generated voice.[1]

Auditory cortical responsiveness has also been found to be suppressed in healthy participants during indirect motor acts such as pressing a button to deliver an auditory tone[6,7,15-18] or recorded speech sounds.[10] It therefore seems as though the responsiveness of the auditory cortex is normatively reduced to self-initiated auditory stimuli, regardless of whether the auditory stimulus is evoked through a direct motor act such as talking, or an indirect motor act such as pressing a button. Similar to the results observed with self-generated vocalizations, patients with schizophrenia have also been found to exhibit subnormal levels of N1-suppression to auditory stimuli evoked by a button press,[17] thus providing further evidence of a general self-suppression deficit in schizophrenia.

Corollary discharges have been hypothesized to travel along frontally extending white matter tracts[19] that primarily consist of myelinated axons.[20] It has been suggested that myelin damage in these frontally projecting white-matter fasciculi could result in temporal delays of the corollary discharges which travel along these fibers,[21] and consequently the misattribution of self-generated actions to external agents.[2] Evidence in support of the "delayed corollary discharge" hypothesis was provided by a study of Whitford et al[22] who found that the N1-suppression abnormalities typically exhibited by schizophrenia patients in response to self-generated, button press elicited tones, could be eliminated by imposing a 50ms, but not a 100ms, delay between the button press and the tone. The authors argued that this might indicate that corollary discharges induced by the button press were delayed by approximately 50ms in the patient group. Additionally, this study found that the degree to which N1-suppression improved as a result of this imposed delay was linearly correlated with the structural integrity of the arcuate fasciculus, as measured with the standard diffusion tensor imaging (DTI) metric of fractional anisotropy (FA). This raised the possibility of the corollary discharges being delayed because of structural damage to the white matter fasciculi connecting the sites of corollary discharge initiation and destination.

Psychotic experiences, including hallucinations and delusions, are commonly associated with psychotic disorders such as schizophrenia. However, a growing body of literature indicates that psychotic-like experiences can also occur in non-clinical members of the general population.[23,24] The term *schizotypy* has been developed to refer to the concept that there exists a "continuum" of psychotic-like experiences extending across the general population.[25-27] According to this concept, individuals vary in terms of their level of schizotypy, and individuals with very high levels of schizotypy may be diagnosed as suffering from a psychotic disorder such as schizophrenia.[28]

If psychotic-like experiences in highly schizotypal individuals are elicited by the same underlying neurophysiological mechanisms as frank psychotic symptoms, then healthy, highly schizotypal individuals would be expected to exhibit similar neurophysiological characteristics to those exhibited by patients with schizophrenia. Studying the neurophysiological basis of psychotic-like experiences also confers some advantages over studying psychotic symptoms *per se*, in that it avoids the clinical confounds typically associated with studying patients with established psychotic disorders, such as neuroleptic medication exposure, illness comorbidities and downward social mobility. Extending this logic to the present study, if delayed corollary discharges are involved in the expression of frank psychotic symptoms, the question arises as to whether this can be generalized to psychotic-like experiences in the healthy population. If this were the case, then N1-suppression to self-generated, undelayed auditory stimuli should (1) also be deficient in highly schizotypal, healthy individuals and (2) be normalized by imposing a delay between the willed action and the resulting sensory feedback.

This proposed rationale was tested in the present study by adopting the button press paradigm used by Whitford et al[22] in a sample of psychologically healthy individuals who scored high and low on the Schizotypal Personality Questionnaire (SPQ),[29] which is a commonly used scale of schizotypy. In addition to the 50ms and 100ms delay conditions previously employed by Whitford et al,[22] the current study also included 25ms and 75ms delay conditions to account for the possibility that the temporal delays present in healthy individuals scoring high on schizotypy might deviate from the temporal delays found in patients with schizophrenia. Based on the aforementioned findings in patients with schizophrenia, it was hypothesized that highly schizotypal individuals would show less N1-suppression to undelayed sounds than individuals who scored low on schizotypy. It was further predicted that imposing a delay between the button press and the sound would eliminate these N1-suppression abnormalities in high schizotypy participants.

Table 1. Demographic Data and Schizotypal Personality Questionnaire (SPQ) Scores of the Participant Groups.

	Low Schizotypy (n = 41)			High Schizotypy (n = 39)			
Variable	Mean	*SD*	Range	Mean	*SD*	Range	Low vs High Schizotypy
Age (years)	20.61	3.23	18-36	21.59	3.31	18-32	$t(78) = 1.34$, $P = .184$
Gender (male/female)	16/25			17/22			$t(78) = -0.41$, $P = .683$
Language (English/non-English)	29/12			19/20			$t(76) = 2.03$, $P = .046$
Household income[a]	41.10	3.00	1-9	30.00	2.52	1-9	$t(58) = -1.52$, $P = .135$
Handedness (right/left)	41/0			37/2			$t(38) = -1.43$, $P = .160$
Caffeine[b]	1.09	1.64	0-9	0.67	0.74	0-3	$t(56) = -1.49$, $P = .143$
Nicotine[c]	0.10	0.63	0-4	0.23	0.67	0-3	$t(78) = 0.92$, $P = .359$
Alcohol[d]	0.76	0.97	0-4	0.72	1.12	0-6	$t(75) = -0.16$, $P = .871$
Recreational drugs	0.17	0.50	0-2	0.21	0.62	0-3	$t(78) = 0.28$, $P = .783$
SPQ total score	9.32	5.49	0-19	35.59	11.77	20-60	$t(53) = 12.69$, $P < .001$
Unusual perceptual experiences	0.61	0.92	0-3	3.08	2.08	0-8	$t(52) = 6.80$, $P < .001$
Suspiciousness	0.98	1.46	0-6	4.26	2.00	0-8	$t(69) = 8.29$, $P < .001$
Odd beliefs or magical thinking	0.46	0.71	0-3	1.82	1.52	0-5	$t(53) = 5.08$, $P < .001$
Ideas of reference	1.29	1.40	0-5	4.85	2.79	0-9	$t(55) = 7.15$, $P < .001$
Excessive social anxiety	1.66	1.89	0-7	5.82	2.10	1-8	$t(78) = 9.32$, $P < .001$
No close friends	0.56	0.74	0-2	4.00	2.41	0-8	$t(45) = 8.55$, $P < .001$
Constricted affect	0.83	1.22	0-5	3.31	2.04	0-7	$t(62) = 6.55$, $P < .001$
Odd or eccentric behavior	1.10	1.81	0-6	2.92	2.30	0-7	$t(72) = 3.93$, $P < .001$
Odd speech	1.78	1.82	0-6	5.44	2.17	1-9	$t(74) = 8.13$, $P < .001$

[a]Household income: 1 = *<$10 000*; 2 = *$10 000-$19 999*; 3 = *$20 000-$29 999*; 4 = *$30 000-$39 999*; 5 = *$40 000-$49 999*; 6 = *$50 000-$74 999*; 7 = *$75 000-$99 999*; 8 = *$100 000-$150 000*; 9 = *>$150 000;* 10 = *Prefer not to say*.
[b]Caffeine: Coffee = *1 unit*, Red Bull = *1.5 units*, Tea, Coca Cola = *0.5 units*.
[c]Nicotine: 0 = *zero*, 1 = *less than 3 per week*, 2 = *less than 5 per week*, 3 = *a pack a week*, 4 = *more than a pack a week*.
[d]Alcohol: 0 = *zero*, 1 = *1-5*, 2 = *6-10*, 3 = *11-15*, 4 = *16-20*, 5 = *21-25*, 6 = *more than 25*.

Method

Participants

Eighty-four participants were recruited through online recruitment systems (SONA and SONA-P) at the University of New South Wales, Sydney, Australia. Participants were reimbursed for their time, either financially or with course credit. Participants' demographic data and scores on the various subscales of the SPQ[29] are presented in Table 1. Exclusion criteria for the study were nonfluency in English, a self-reported diagnosis of an axis I disorder based on *DSM-IV-TR* criteria[30] and a self-reported family history of schizophrenia. Four participants were excluded from the analysis due to a self-reported diagnosis of an axis I disorder based on *DSM-IV-TR* criteria.[30] Participants were divided into Low (n = 41) and High (n = 39) Schizotypy (SZPY) groups based on a median split of their scores on the SPQ. As shown in Table 1, the High and Low SZPY groups were matched on age, gender, handedness, household income as well as caffeine, nicotine, and alcohol consumption. After outlining the procedure of the study and providing an opportunity to ask questions for clarification, all participants gave written informed consent to participate. This study was approved by the University of New South Wales Human Research Ethics Advisory Panel (Psychology).

Materials and Procedure

The procedure was based on the design described by Whitford et al.[22] Participants were seated in a quiet, dimly lit room, 1m in front of a computer monitor (BenQ XL2420T, 144Hz, 24 inches wide), on which they completed a series of questions relating to their demographic information, followed by the SPQ. Participants then underwent EEG recording.

The electrophysiological component consisted of the 3 experimental conditions, termed Active, Listen, and Motor. Each condition was preceded by a practice trial in order to provide participants the opportunity to familiarize themselves with the task. In the Active condition, participants were asked to press a button at will on a response pad (Cedrus Corporation, Model RB-530), while focusing on a fixation cross, displayed on the monitor. Following the button press, a pure tone (duration = 100ms; frequency = 500Hz; sampling rate = 44,100Hz) was played to participants through headphones (Shintaro, 100-15,000Hz, 32ohm, 101dB 4dB, 100mW). The Active condition consisted of 5 delay conditions. In the 0ms condition, the tone was presented to the participant immediately following the button press. In the 25ms delay condition, the tone was played 25ms following the button press, and similarly for the 50ms, 75ms, and 100ms delay conditions. Each delay condition was delivered as a single block of 60 trials. The order of the blocks was randomized for each participant. After each block, participants had the opportunity to rest before proceeding with the next block.

These 5 Active conditions were each compared to the Listen condition, in which participants were instructed to focus on a fixation cross on the computer screen, while listening to a series of tones, which were identical to the tones in the Active

conditions and played back through headphones. Each tone was played 1 to 2 seconds following the presentation of a fixation cross. This interstimulus interval was chosen to match the typical interstimulus intervals in the Active conditions. The listen condition consisted of a single block of 60 trials.

The Motor condition was similar to the Active conditions in that participants were instructed to press a button at will on a response pad while focusing on a fixation cross; however, pressing the button did not result in a tone being played. The Motor condition consisted of a single block of 60 trials. The Motor condition was included in order to enable the subtraction of the EEG activity elicited by the button press from the EEG activity evoked by the sound, as is typical in experiments of this nature.[6,10]

In the Active and Motor conditions, participants were instructed to fixate on the central fixation cross on the screen and to press the button on the response pad "whenever you feel like it". In the Active conditions, participants were informed that "Pressing the button will cause a sound to play. Your task is simply to press the button and listen to the resulting sound." For the Listen condition, participants were instructed to fixate their eyes on the central fixation cross, and to "sit back, relax and listen to the sounds."

The order of the 7 experimental conditions (ie, 5 Active conditions, Listen, Motor) was randomized for each participant. This was done in order to control for the possibility that participants would habituate to the sound of the tone over the course of the testing session.

Data Acquisition and Analysis

Throughout the experiments EEG was recorded with a BioSemi ActiView system (2048Hz sample rate, 417Hz bandwidth [3dB], 18dB/octave roll-off), using an electrode cap with Ag/AgCl electrodes from 64 sites referenced to internal sensors located in the parietal lobe of the cap (version 1.0, www.biosemi.com). Data were referenced off-line to the mastoid electrodes during pre-processing. Additional electrodes were placed on the outer canthi of both eyes and below the left eye to measure eye blinking and movement (vertical and horizontal electro-oculogram; VEOG, HEOG). EEG data were analyzed using the BrainVision Analyzer 2 software package (Biosemi, Amsterdam, Netherlands). The EEG data were segmented into 700ms intervals, consisting of 100ms preceding and 600ms following the stimulus. A regression-based algorithm was adopted to correct for eye blinks and movements in the EEG using VEOG and HEOG.[31] Low and high frequencies were attenuated using a 0.5- to 15-Hz bandpass filter, as has been used previously.[17,22] Trials containing motor artifacts, defined as voltages exceeding ±50μV, were rejected. The remaining artifact free trials in the Listen, Active and Motor conditions were averaged to event-related potentials (ERPs) for each participant respectively. The N1-component of each ERP was identified as the most negative peak between 75ms and 125ms after sound onset. ERPs were baseline corrected to the average voltage of the 100ms prestimulus period. N1-amplitudes were reported for electrode Cz because of its characteristically large N1-amplitude elicited by bilateral auditory stimulation.[22]

Statistical Analysis

Statistical analysis was performed using SPSS (version 21, www.spss.com). As is typical in studies investigating N1-suppression,[10,22] N1-suppression was calculated by first calculating a 'motor-corrected' Active value for each condition, by subtracting the Motor condition from the Active condition. This 'motor-corrected' Active value was then subtracted from the Listen condition. In other words:

$$N1_{Suppression} = N1_{Listen} - \left(N1_{Active} - N1_{Motor}\right)$$

In order to examine the effect of condition on N1-amplitude at electrode Cz, a 2 × (5) mixed analysis of variance (ANOVA) was conducted, with the between-group factor being *group* (High SZPY/Low SZPY) and the within-group factor being *condition* (0ms/ 25ms/ 50ms/ 75ms/ 100ms). For testing the significance of the main effects and interaction, the critical α was set to .05. In the case of a significant main effect of group, follow-up *t*-tests were used to identify the underlying simple effects. To control for α-inflation due to multiple comparisons, the critical α-value for the supplementary between-group *t*-tests was adjusted to .05/5 = .01, using the Bonferroni procedure.

Results

The mean score on the SPQ of the overall sample was 22.13 (SD = 16.02, range = 0-60), and the median was 19. A median split was used to define the Low SZPY group as the 41 participants scoring ≤ 19 on the SPQ (M = 9.32, SD = 5.49). The High SZPY group were defined as the 39 participants scoring above 19 on the SPQ (M = 35.59, SD = 11.77; see Table 1).

The ERP waveforms showing the N1-amplitude of the 5 (motor-corrected) Active conditions and the Listen condition for the High and Low SZPY groups are presented in Figure 1. Mean level of N1-suppression (± SEM) over the 5 (motor-corrected) Active conditions for High and Low SZPY groups are presented in Figure 2. An omnibus ANOVA revealed a significant main effect for *condition* (0ms/ 25ms/ 50ms/ 75ms/ 100ms) on the level of N1-suppression at electrode Cz, $F(4, 312) = 19.559$, $P < .001$, $\eta^2 = 0.200$. The main effect of *group* (High SZPY/Low SZPY) was also significant, $F(1, 78) = 4.410$, $P = .039$, $\eta^2 = 0.054$. Finally, there was also a significant *group* × *condition* interaction, $F(4, 312) = 3.632$, $P = .015$, $\eta^2 = 0.044$.

Supplementary *t*-tests were used to identify the simple effects underlying the main effect of *group*. The *t*-tests revealed that the High SZPY group exhibited significantly less N1-suppression in the 0ms condition, $t(78) = 2.942$, $P = .004$, and the 25ms condition, $t(78) = 2.684$, $P = .009$, compared with

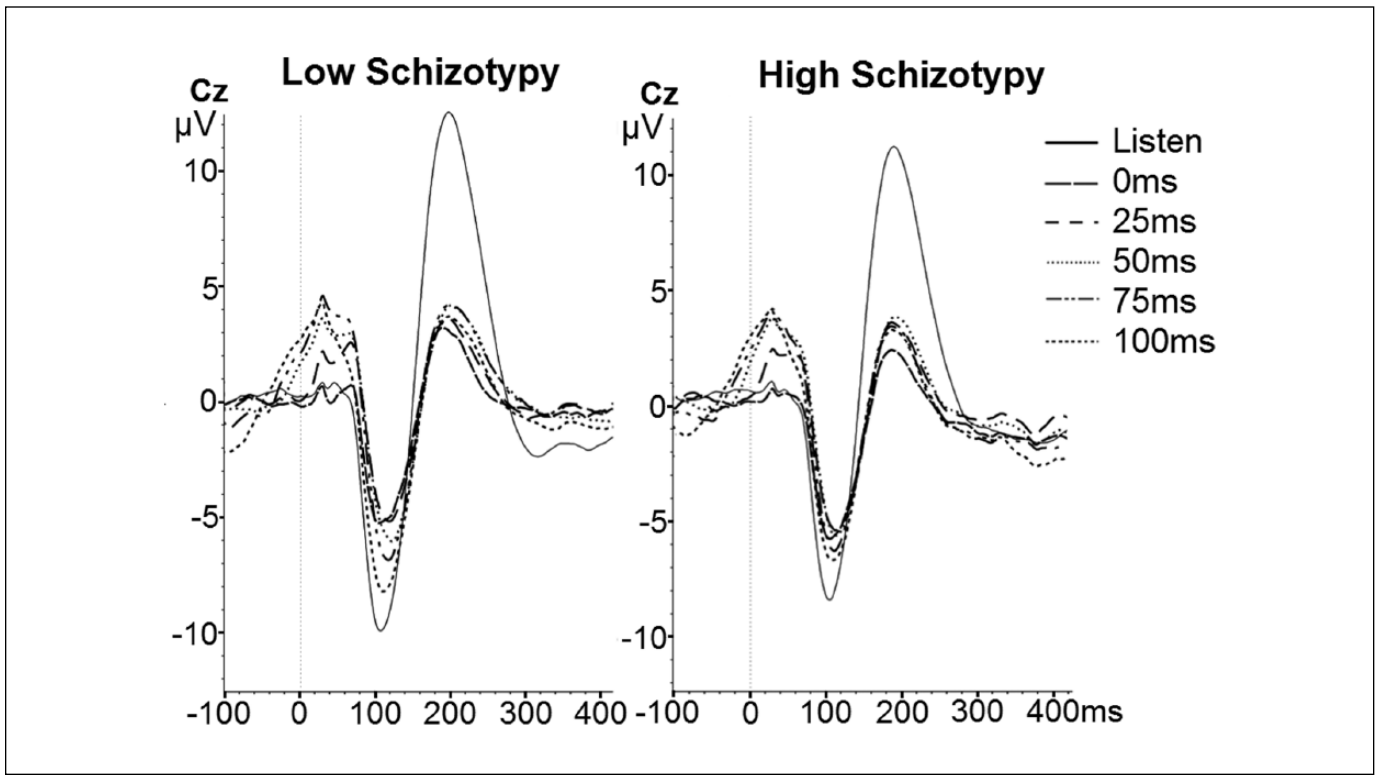

Figure 1. Event-related potentials (ERPs) from electrode Cz for the Listen and 0ms, 25ms, 50ms, 75ms, and 100ms delay conditions, separated for the Low Schizotypy and High Schizotypy groups. ERPs for the delay conditions are calculated by subtracting the motor condition from the active conditions. The *x*-axis represents time in milliseconds (ms) and the *y*-axis amplitude in microvolts (μV).

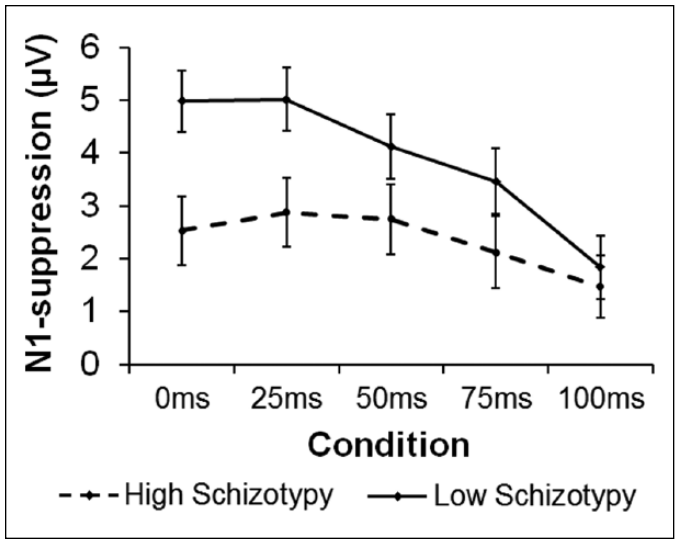

Figure 2. The relationship between delay condition (ie, the duration of the imposed delay between a willed button press and the delivery of an auditory tone: 0 ms/25 ms/50 ms/75 ms/100 ms) and amount of N1-suppression (in microvolts, μV) at electrode Cz for the High Schizotypy and Low Schizotypy groups. Error bars represent standard errors of the mean.

the Low SZPY group at the corresponding delay conditions. The level of N1-suppression between the High and Low SZPY groups was not significantly different in the 50ms condition, $t(78) = 1.684$, $P = .096$, the 75ms condition, $t(78) = 1.544$, $P = .127$, or the 100ms condition, $t(78) = 0.557$, $P = .579$.

To identify the cause of the significant *group* × *condition* interaction, repeated-measures ANOVAs were conducted separately for each group. These analyses revealed a significant main effect of *condition* in the Low SZPY group, $F(4, 160) = 21.653$, $P < .001$, $\eta^2 = 0.351$, and a significant main effect of *condition* in the High SZPY group, $F(4, 152) = 3.322$, $P = .034$, $\eta^2 = 0.080$. In the Low SZPY group, supplementary *t*-tests revealed a significant difference between N1-suppression in the 0ms condition compared with the 50ms condition, $t(40) = 2.057$, $P = .046$, and the 25ms condition compared with the 50ms condition, $t(40) = 3.056$, $P = .004$, but no significant difference between the 0ms and 25ms conditions, $t(40) = 0.641$, $P = .525$. In the High SZPY group, follow-up *t*-tests revealed no significant differences between the 0ms condition compared with the 25ms condition, $t(38) = 0.959$, $P = .344$, or the 50ms condition, $t(38) = 0.454$, $P = .652$, or between the 25ms condition and the 50ms condition, $t(38) = 0.431$, $P = .669$.

The extent to which the *condition* factor followed linear and quadratic trends was also explored separately for each group. In the Low SZPY group, the change in N1-suppression over the 5 delay conditions was best described by a linear trend, $F(1, 40) = 45.448$, $P < .001$, $\eta^2 = 0.532$. In contrast, in the High SZPY group, the change in N1-suppression over the 5 delay conditions was best described by a quadratic trend, $F(1, 38) =$

6.594, $P = .014$, $\eta^2 = 0.148$, with the linear trend being nonsignificant, $F(1, 38) = 3.664$, $P = .063$, $\eta^2 = 0.088$. Furthermore, when the magnitude of the linear trend was compared between the 2 groups, the *group* × *condition* interaction was found to be significant, $F(1, 78) = 6.859$, $P = .011$, $\eta^2 = 0.081$. This indicated that the extent to which the change in N1-suppression over the 5 delay conditions reflected a linear trend differed between the High and Low SZPY groups.

Supplementary Analyses of "Normalized" Suppression Scores

A significant between-group difference was observed in N1-amplitude in the Listen condition, $F(1, 78) = 4.748$, $P = .032$, $\eta^2 = 0.57$. This raised the question of whether the observed between-group differences in N1-suppression were a secondary consequence of "baseline" differences in N1-amplitude. To test this, a *z*-transformation was used to normalize each participant's score across the 6 conditions (ie, Listen and 5 corrected Active conditions). This was done separately for each group such that each group's average score across the 6 conditions was 0, and the standard deviation was 1. This 'normalized' suppression score was then analyzed using the same mixed-model ANOVA design described previously for the analysis of the raw data. The results of the analysis with the 'normalized' data were comparable (and slightly stronger) to the analysis of the raw data; specifically, the main effect of *group* remained significant, $F(1, 78) = 6.299$, $P = .014$, $\eta^2 = 0.075$, the main effect of *condition* remained significant, $F(4, 312) = 20.413$, $P < .001$, $\eta^2 = 0.207$, and the *group* × *condition* interaction remained significant, $F(4, 312) = 4.484$, $P = .005$, $\eta^2 = 0.054$. These results suggest that the observed between-group differences in N1-suppression were not driven by the observed group differences in N1-amplitude to the Listen condition.

Discussion

The first aim of the present study was to investigate whether healthy individuals who scored highly on the personality dimension of schizotypy exhibited subnormal levels of N1-suppression to undelayed, self-initiated, button press elicited auditory stimuli, such as has previously been reported in patients with established schizophrenia.[17,22] The results supported this first prediction: nonclinical individuals who scored above the median on the SPQ (the High Schizotypy group) showed significantly less N1-suppression to undelayed, button press elicited tones than individuals who scored below the median on the SPQ (the Low Schizotypy group). The second aim of the study was to investigate whether delaying the onset of the tone following the button press would eliminate these N1-suppression abnormalities in High Schizotypy participants. The results of the study did not provide support for this hypothesis; delayed tones did not elicit significantly higher levels of N1-suppression compared with undelayed tones in the High Schizotypy group. However, the results did suggest that delaying the onset of the tone had a differential effect on N1-suppression in the High Schizotypy participants compared with the Low Schizotypy participants, as illustrated by the significant *group* × *condition* interaction in the magnitude of the linear trend across delay conditions. In summary, the results of the present study suggest that N1-suppression abnormalities to self-initiated, button press elicited auditory stimuli are not unique to schizophrenia but are instead associated with high schizotypy more generally, and thereby provide support for the concept of a neurophysiological "continuum of psychosis".[26,27]

The findings of the present study are broadly consistent with previous research in the tactile domain. Blakemore et al[32] investigated whether imposing a delay (of 100-300ms) between the initiation of a willed action and resultant tactile stimulation would modulate healthy participants' subjective ratings of perceived ticklishness. The tactile stimulus was produced on the palm of the right hand by means of a piece of foam attached to a robotic arm. The robotic arm could either be moved by participants' left hand in the self-generated condition or by a computer in the externally generated condition. Participants were trained to produce the same amplitude and frequency of movement as the computer. Throughout the experiment, participants were instructed to rate the intensity of the sensation on their right palm on a 10-point rating scale. Consistent with the results of the Low Schizotypy group in the present study, Blakemore et al[32] found a linear association between delay period and subjective ratings of "ticklishness"; that is, self-produced movements were rated as more ticklish the longer the delay period between the movement and the tactile stimulation. Taken together with the results of the present study, this finding suggests that artificially imposing a delay between a willed action and the resulting sensory feedback leads to (1) a reduction in sensory suppression and (2) self-generated sensations being processed as though they were externally generated, both phenomenologically (as per the results of Blakemore et al[32]) and electrophysiologically (as per the results of the present study).

Numerous previous studies have reported neuropsychological and neurophysiological irregularities in nonclinical, highly schizotypal individuals that are reminiscent of those reported in patients with established schizophrenia, including abnormalities in attention,[33] working memory,[34,35] executive functioning,[36] and perceptions of agency.[37-39] However, abnormalities in self-suppression have been argued to be of particular significance as they provide a direct and plausible explanation of the most characteristic clinical features of schizophrenia, such as passivity experiences and auditory hallucinations.[1,2] Our finding that the High Schizotypy group exhibited N1-suppression deficits to undelayed button press elicited tones is consistent with previous findings in patients with established schizophrenia[22] and suggests that self-suppression abnormalities may be associated with high schizotypy *generally* as opposed to schizophrenia *specifically*. Further support for this idea is provided by Ford et al,[40] who found that bipolar patients and the first degree relatives of patients with schizophrenia both exhibited levels of N1-suppression to undelayed, button press elicited tones that were intermediate between the level of N1-suppression exhibited by patients with established schizophrenia and those exhibited by healthy controls without a family history of psychotic disorders. The fact that high levels of schizotypy are one

of the primary risk factors associated with transition to psychosis in high-risk individuals provides further support for an association between schizotypy and psychotic disorders. For example, a significant proportion of the Ultra-High Risk cohort defined by the PACE Clinic at ORYGEN, Melbourne were classified on the basis of high schizotypy (the Attenuated Psychotic Symptoms group).[41]

With regard to the underlying cause of these self-suppression deficits, the present study provided some support for the theory of Whitford et al,[22] who suggested they may be underpinned by temporally delayed corollary discharges. In the present study, an inverse linear function best described the effect of increasing temporal delays on N1-suppression in the Low Schizotypy group; that is, increasing delay periods were associated with decreasing levels of N1-suppression, consistent with the aforementioned findings of Blakemore et al.[32] In contrast, a quadratic function best described the same data in the High Schizotypy group. While this result is not inconsistent with the suggestion that the N1-suppression abnormalities exhibited by the High Schizotypy group were caused by delayed corollary discharges, it must be emphasized that there were no statistically significant differences between level of N1-suppression in the 0ms, 25ms, and 50ms delay conditions in the High Schizotypy group. Nonetheless, the statistical significance of the *group* × *condition* interaction indicated delaying the onset of the tone had a differential effect on N1-suppression in the high schizotypes compared with the low schizotypes.

In light of the fact that N1-suppression abnormalities have previously been identified in high-risk participants in response to willed vocalizations,[42] the results of the present study open up the possibility that N1-suppression patterns to delayed sensory feedback could be used to predict transition to psychosis in high-risk individuals. Additionally, it is also conceivable that an individual's level of N1-suppression to delayed sensory feedback could be modified with repeated exposure to delayed sensory feedback. While speculative, such a result would have major implications with regard to developing novel treatments for psychotic illnesses; for example, it would raise the possibility of behaviorally "training" the N1-suppression levels of psychotic individuals by systematically exposing them to delayed feedback of self-generated auditory stimuli. Furthermore, if some psychotic symptoms arise from self-suppression abnormalities (as has previously been suggested),[1,2] such behavioral training could also potentially be clinically therapeutic.

Considering that one of the key aims of the present study was to assess N1-suppression abnormalities with respect to a neurophysiological "continuum of psychosis", the absence of a clinical group was a limitation. However, it should be noted that previous studies that have used clinical participants have reported similar scores on the SPQ[43] such as were observed in the High Schizotypy group in the present study (M = 35.6, SD = 11.8). For example, Cadenhead et al[43] reported SPQ scores comparable to ours in their sample of patients with schizotypal personality disorder (M = 34.5, SD = 11.10) and schizophrenia (M =30.9, SD = 16.9). Nevertheless, while the results of the present study indicated that N1-suppression abnormalities are present in nonclinical, unmedicated highly schizotypal individuals, a direct comparison of the effects of delaying sensory feedback on N1-suppression between highly schizotypal, nonclinical individuals and patients with established schizophrenia is lacking at this stage and would, we suggest, represent a fruitful area for future research.

In summary, the results of the present study indicated that nonclinical, highly schizotypal individuals exhibited subnormal levels of N1-suppression to undelayed, button press elicited tones, relative to low schizotypes. Furthermore, imposing a delay between the button press and the resulting tone was found to have a differential effect on N1-suppression between high and low schizotypes. To the extent that this pattern of results resembles the N1-suppression abnormalities that have previously been reported in patients with schizophrenia,[17,22] the findings of this study are consistent with the notion of a neurophysiological "continuum of psychosis."[26,27]

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Author Contributions

Lena Oestreich and Nathan Mifsud collected the data for the study. Lena Oestreich performed the literature review, analyzed the EEG data, performed the statistical analysis and wrote the first draught of the manuscript under the supervision of Dr. Thomas Whitford. Dr. Thomas Whitford designed the study, obtained funding, provided resources and EEG equipment, assisted with the data analysis and writing of the manuscript. Prof. Judith Ford, Prof. Daniel Mathalon and Brian Roach assisted with the design of the study, provided advice and assistance with the EEG analysis and the interpretation of the results. All authors contributed to the writing of the final manuscript.

Authors' Note

This work is part of Lena Oestreich's doctorate thesis (PhD).

Declaration of Conflicting Interests

The authors declared the following conflicts of interest with respect to the research, authorship, and/or publication of this article: Prof. Daniel Mathalon serves as a consultant for Roche and Amgen. All remaining authors declare that there are no conflicts of interest.

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