Original Article

Sensory Gating Deficits and their Clinical Correlates in Drug-Free/Drug-Naive Patients with Schizophrenia

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ABSTRACT

Background: Sensory gating refers to "filtering" of irrelevant sensory input in the brain. Auditory sensory gating deficit has been considered as a marker of schizophrenia (SCZ) and assessed using P50 paired-click paradigm. We explore sensory gating deficits and their clinical correlates in SCZ. **Materials and Methods:** Twenty-five drug-free/drug-naïve patients with SCZ, whose psychopathology was assessed using Positive and Negative Syndrome Scale (PANSS), and 25 age-matched normal controls (NC) were recruited. ERP recordings were done using 40-channel event-related potential measuring system. **Results:** S2-S1 P50 amplitude difference, an index of sensory gating, was significantly lower in SCZ at F3 and F4 sites when compared to NC, indicating impaired gating. SCZ had significantly lower S1 amplitude compared to NC at these sites; S2 amplitudes were comparable. The sensory gating index also showed significant correlations with PANSS scores. **Conclusions:** Our study reiterates sensory gating abnormalities in SCZ and confers a frontal specificity, implying specific deficits in early preattentive processes to them. Further, we suggest that gating deficits in SCZ are driven predominantly by abnormally small S1 rather than an inability to suppress S2. A correlation between sensory gating parameters and measures of psychopathology strengthens the hypothesis that abnormal response to sensory input may contribute to the psychopathology in SCZ.

Key words: *Event-related potential, P50, schizophrenia, sensory gating*

INTRODUCTION

The endophenotype construct represents a promising approach in studying the etiological and therapeutic underpinnings of schizophrenia (SCZ), which is among the top ten leading causes of disease-related disability

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in the world.[1] Gottesman and Gould introduced the concept of "endophenotypes."[2] Ritsner and Gottesman define them as "quantifiable biological variations or deficits that are types of stable trait markers or indicators of presumed inherited vulnerability or liability to a disease."[3] A search for potential endophenotypes has led to the discovery of deficits in both the early preattentive stage and later evaluative processes of information processing in patients with SCZ.[4,5] Sensory gating denotes the function of "filtering" irrelevant sensory input in the brain.[6,7] It is one of the elementary mechanisms that the brain uses to organize and prioritize the salience of incoming stimuli, and it is speculated that individuals with SCZ cannot gate irrelevant sensory input, leading to an overload of information reaching the consciousness.[7-9] It has been hypothesized that deficits in sensory gating may result from neuronal hyperexcitability due to aberrant inhibitory pathways in cortical and subcortical areas of the brain.[10,11]

Classically, attenuation of the response to the second stimulus in a pair of stimuli, under conditioning testing paradigms, has been used to reflect the strength of the inhibitory pathway.[12] This phenomenon, better known as "sensory gating," is assessed using an auditory P50 paired-click paradigm while recording electroencephalogram.[5,10,11,13] In this, two identical auditory stimuli are presented as pairs 500 ms apart. The P50 wave is the most positive peak, approximately 40–90 ms after each auditory click.[13,14] A reduction in the amplitude of the P50 wave in response to the second of the two paired auditory stimuli reflects a sensory gating mechanism and is termed as "P50 suppression."[11,13]

A lower P50 suppression, i.e., deficit in sensory gating, has been extensively reported among patients with SCZ.[10,15-21] Meta-analyses of studies on P50 waveforms in SCZ showed a significant difference in the gating ratio between patients with SCZ and controls. While Bramon *et al*. (2004)[22] reported a pooled standardized effect size of 1.56 (95% confidence interval [CI]: 0.05–1.06; $P < 0.001$) for a higher P50 ratio in SCZ patients compared to controls, Patterson *et al*.[23] showed that the average difference in the P50 gating ratio across studies was 45.8% (95% CI: 38.2%–53.4%), with SCZ patients showing significantly greater P50 ratios. Moreover, Su *et al*.[24] reported P50 ratio in SCZ group to be significantly higher than the normal control (NC) group ($Z = 11.46$, $P < 0.00001$, combined standardized mean difference = 44.18, 95% CI: 36.62–51.74).

Although P50 ratio (S2/S1) has been traditionally used, more recent studies have preferred S1−S2 difference as a more reliable index of sensory gating. As the shared variance between S1 and S2 cannot be completely eliminated, the P50 ratio has greater variability and lacks reliability.[25-27] Earlier, Smith *et al*.[25] and, more recently, Dalecki *et al*.[28] evaluated various P50 paired-click methodologies and suggested that S1−S2 difference as an index of sensory gating has more power to detect effects. Many studies with SCZ patients have subsequently used P50 S1−S2 difference scores.[5]

More recently, Schubring *et al*. (2018),[20] using magnetoencephalography, showed that S1–S2 difference as an index of sensory gating was significantly lower in SCZ patients compared to healthy controls, with medium-to-large effect sizes. Moreover, this study also found that abnormal sensory gating is present and is not significantly different between the first-admission and chronic SCZ patients. A recent study by Micoulaud-Franchi *et al*.[29] suggested that sensory gating deficit (P50 amplitude change) is a determinant of impaired quality of life in SCZ. More importantly, recent investigations have also used P50 suppression as a treatment biomarker for brain stimulation in SCZ.[30]

In this study, we aimed to compare sensory gating in drug-free or drug-naïve patients with SCZ and NCs using P50 paired-click paradigm. Replication of gating deficits in an Indian sample would further add to the literature on sensory gating and strengthen the claim of P50 as a potential electrophysiological marker in SCZ.

MATERIALS AND METHODS

Study design and participants

This study was conducted at the K. S. Mani Centre for Cognitive Neurosciences at Central Institute of Psychiatry (CIP), Ranchi. It was a hospital-based cross-sectional study using convenience sampling. Twenty-five individuals of either gender, aged between 18 and 60 years, who met the International Statistical Classification of Disease-10 diagnostic criteria for research (DCR) diagnostic criteria for SCZ (F20), and who were drug naïve or drug free (free of oral neuroleptics for at least 4 weeks, or free of depot antipsychotics for 12 weeks) were recruited between January 2012 and June 2012. Individuals with a history of any comorbid substance abuse, including nicotine in any form, were excluded as substances can influence sensory gating. Individuals with any clinically significant medical or neurological disorder were also excluded. Twenty-five controls were recruited from the healthy staff and postgraduates of CIP, Ranchi. Controls were screened using the General Health Questionnaire[31] (score below 3), and they were included in the study only if they reported no personal history of psychiatric disorder or a personal history of substance abuse. All

the participants, including patients with SCZ and controls, were right handed which was confirmed using Sidedness Bias Schedule.[32] Normal hearing ability was confirmed in all the participants, with Rinne, Weber, Bing, and Schwabach tests at the bedside. Ethical clearance was obtained from the Institutional Review Board of Central Institute of Psychiatry, Ranchi, and all the participants gave written informed consent. Positive and Negative Syndrome Scale (PANSS)[33] was used to assess psychotic symptoms in the SCZ group.

Event-related potential recording

Event-related potential (ERP) recordings of all the participants were done using 40-channel, evoked potential measuring system (Ebneuro Galileo Mizar 40) using Galileo NT ERP software(Ebneuro, Florence, Italy). The P50 paradigm was recorded from 40 electrode positions in which two identical sound "clicks" were presented to the patient. Stimuli were 40 ms, 80 dB clicks (1000 Hz, 4 ms rise and fall times) presented binaurally through headphones. The interstimulus interval between S1 and S2 was 500 ms, and the interval between two consecutive pairs was 8–10 s, allowing full recovery of the auditory-evoked potential. In total, 50 stimulus pairs were presented that last around 9 min. The patients were instructed to listen passively to the clicks and to relax and sit quietly with their eyes open while fixing their gaze on a fixation cross.

Electrode positioning was done using the 10–20 system of electrode placement. The reference electrodes were placed on both the mastoids. The ground electrode was placed on prefrontal midline (Fpz). The impedance of all electrodes was under 5 kΩ.

P50 event-related potential back averaging

The P50 wave, generated for each of the paired clicks (S1 and S2), was defined as the most positive peak between 40 and 90 ms after click onset[14] and was measured from the peak to the preceding trough.[22] P50 waves were marked by visual inspection method by two independent investigators blind to the diagnostic status after automatic artifact rejection and back averaging. S1 amplitude and latency and S2 amplitude and latency were noted. Most studies have assessed sensory gating at Cz site, but in our study, we evaluated it at additional sites around Cz site, namely frontal (F3, Fz, F4), fronto-central (FC3, FCz, FC4), central (C3, Cz, C4), centro-parietal (CP3, CPz, CP4), and parietal (P3, Pz, P4). S1 minus S2 amplitude difference was taken as a measure of sensory gating. Specifically, for calculation of this relative measure, the missing values (P50 being not identifiable at a respective electrode for a respective patient) were replaced by "0."

Statistical analysis

Statistical analysis was done using the Statistical Package for the Social Sciences version 16(IBM Corporation, New York, USA). Chi-square and Fisher's exact tests were applied for comparison of categorical sociodemographic and clinical variables among groups. Independent samples *t*-tests were applied to compare continuous sociodemographic variables between the groups. Most P50 variables were found to be not normally distributed on the Shapiro–Wilk test, predominantly due to violation of kurtosis. Hence, nonparametric tests – Mann–Whitney U-test for comparison and Spearman's test for correlation – were performed. Multivariate analysis of variance (MANOVA) is traditionally considered "robust" and less sensitive to violations in its various assumptions that include normality of data.[34] And moreover, a very recent review by Cain *et al*.[35] suggested that MANOVA has a lesser influence of kurtosis, specifically. Hence, to study the interaction effects, a MANOVA with two within-group factors – (a) Regions (five – frontal, frontocentral, central, centroparietal, and parietal), (b) Laterality (three – left, midline, and right), and a between-group factor – Group (two – patient and control) was conducted. Partial correlations were conducted using specific confounding variables. All *P* values are two tailed, and the significance level was set to $P < 0.05$. Bonferroni corrections for multiple comparisons were applied where applicable.

RESULTS

Background characteristics of the subjects

As depicted in Table 1, the two groups did not differ in terms of mean age, sex, marital status, religion, or premorbid personality. However, the SCZ group had significantly lower number of years of education ($t = -3.094$, df = 48, $P = 0.003$). The groups differed significantly in socioeconomic class ($\chi^2 = 23.529$, df = 1, $P < 0.001$), with all the patients in the SCZ group belonging to lower socioeconomic class, whereas nine participants in the control group belonged to lower socioeconomic class and 16 belonged to middle socioeconomic class. The groups also had a significant difference in terms of family history of psychiatric disorders ($\chi^2 = 10.965$, df = 1, $P = 0.001$), with 11 participants in the SCZ group having a family history of psychiatric disorders compared to one in the control group.

Clinical characteristics and psychopathology in schizophrenia group

As depicted in Table 1, nearly half of the patients in the patient group were diagnosed with paranoid SCZ (48%) followed by undifferentiated SCZ (28%), SCZ unspecified (20%), and catatonic SCZ (4%).

Table 1: Demographic and clinical variables of patients with schizophrenia and controls

Characteristics	Schizophrenia (*n*=25)	Controls (*n*=25)	t/χ^2	*P*
Age, years (mean±SD)	31.08±6.01	31.04±5.15	0.025	0.98†
Years of education (mean±SD)	7.44±5.20	12.48±6.26	−3.094	0.003†,**
Sex (*n*)				
Male/female	22/3	22/3	-	1‡
Marital status (*n*)				
Married/unmarried	15/10	14/11	0.082	0.774§
Socioeconomic status (*n*)				
Lower/middle	25/0	9/16	23.529	<0.001§,**
Religion (*n*)				
Hindu/others	20/5	20/5	0	1§
Family psychiatric history (*n*)				
Absent/present	14/11	24/1	10.965	0.001§,**
Premorbid personality (*n*)				
Well adjusted/schizoid	22/3	25/0	-	0.235‡
Drug status (*n*)				
Drug free/drug naive	16/9			
Diagnosis (*n*)				
Paranoid schizophrenia	12			
Undifferentiated schizophrenia	7			
Schizophrenia unspecified	5			
Catatonic schizophrenia	1			
PANSS score (mean±SD)	72.96±11.2			
Positive score	19.28±4.45			
Negative score	20.6±6.03			
General score	33.08±6.89			

†Independent samples *t*-test; ‡Fisher's exact test, §Chi-square test; **Statistically significant at the 0.01 level (two tailed). PANSS – Positive and Negative Syndrome Scale; SD – Standard deviation

P50 variables

S1 amplitudes in the SCZ group were significantly (using uncorrected *P*) smaller than the control group at the following locations: F3, FZ, F4, FC3, FCZ, FC4, and CZ. Controlling for multiple comparisons, when reviewed at $P < 0.0033$ (i.e., 5/15), the significant difference survived only at F3 and F4 [Supplementary Table S1]. On comparison of mean S2 amplitudes of SCZ group and control group, no significant difference (even uncorrected *P*) was found between the groups at any of the locations [Supplementary Table S2].

Significantly (using uncorrected *P*) longer latencies were found in the patient groups for S1 at locations FC4, CZ, and CPZ and for S2 at P3. Controlling for multiple comparisons, when reviewed at $P < 0.0033$ (i.e., 5/15), the significant difference survived only for S2 at P3 (Supplementary Tables S3 and S4).

MANOVA with two within-group factors – a) Regions (five – frontal, frontocentral, central, centroparietal, and parietal), b) Laterality (three – left, midline, and right) – and a between group factor – Group (two – patient and control) for "S1 minus S2" values found a significant effect of regions (Pillai's trace $F = 2.757$; $P = 0.039$; partial $\eta^2 = 0.197$; observed power = 0.713), regions × laterality (Pillai's trace $F = 3.083$; $P = 0.008$; partial $\eta^2 = 0.079$; observed power = 0.396) and regions × groups (Pillai's trace $F = 5.34$; $P = 0.001$; partial $\eta^2 = 0.322$; observed power = 0.957). Table 2 shows the comparison of S1 minus S2 values of SCZ and control groups. The values were significantly (using uncorrected *P*) smaller in the patient group at F3, Fz, F4, FC3, FC4, and CP4. Controlling for multiple comparisons, when reviewed at $P < 0.0033$ (i.e., 5/15), the significant difference survived only at F3 and F4.

Clinical correlates of P50 sensory gating parameters in schizophrenia

While S1–S2 difference at F4 significantly negatively correlated with age and PANSS positive scores, S1–S2 difference at F3 significantly negatively correlated with PANSS general psychopathology and total scores. When diagnostic subtype was added as a covariate in the analysis, the significant correlation of S1–S2 at F4 with age did not survive, while the rest survived [Table 3].

DISCUSSION

We set out to evaluate sensory gating functions in drug-free or drug-naïve patients with SCZ and compare them with healthy controls. Both the groups were similar in terms of age, gender distribution, and premorbid personality. However, SCZ group had lower

Table 2: Comparison of S1-S2 gating index of schizophrenia and control groups

	Schizophrenia (*n*=25)		Control (*n*=25)		*Z*	*P*
	Mean±SD	Mean rank	Mean±SD	Mean rank		
Frontal						
F3	0.07±1.42	18.62	2.15±2.30	32.38	−3.338	0.001**,#
FZ	0.11±1.16	19.84	1.68±2.16	31.16	−2.754	0.006**
F4	0.00±1.63	18.72	2.14±2.30	32.28	−3.289	0.001**,#
Fronto-central						
FC3	0.09±1.00	20.74	1.09±1.72	30.26	−2.310	0.021*
FCZ	0.23±0.84	23.20	0.76±1.34	27.80	−1.116	0.265
FC4	0.22±1.24	20.58	1.43±1.74	30.42	−2.387	0.017*
Central						
C3	0.16±0.66	24.08	0.38±1.22	26.92	−0.689	0.491
CZ	0.34±0.65	22.14	0.81±1.22	28.86	−1.630	0.103
C4	0.04±0.97	21.58	0.86±1.55	29.42	−1.902	0.057
Centro-parietal						
CP3	0.14±0.62	25.98	−0.06±1.23	25.02	−0.233	0.816
CPZ	0.38±0.56	27.04	0.20±0.86	23.96	−0.747	0.455
CP4	−0.04±1.17	21.20	0.57±1.06	29.80	−2.086	0.037*
Parietal						
P3	0.01±1.10	23.60	0.47±1.62	27.40	−0.922	0.357
P4	−0.15±0.88	23.28	−0.04±1.27	27.72	−1.077	0.282
PZ	−0.14±1.68	25.48	0.34±1.80	25.52	−0.010	0.992

Mann–Whitney test was used to test the differences between schizophrenia group and control group. *Statistically significant at the 0.05 level (two tailed); **Statistically significant at the 0.01 level (two tailed); #Statistically significant at the 0.0033 level (Bonferroni correction for multiple comparisons). SD – Standard deviation

Table 3: Significant correlations between sensory gating variables and Positive and Negative Syndrome Scale scores

S1-S2	Age		PANSS positive scale		PANSS general psychopathology		PANSS total score	
	Bivariate	Partial$	Bivariate	Partial$	Bivariate	Partial$	Bivariate	Partial$
F3					−0.420* (0.037)	−0.497* (0.014)	−0.520* (0.008)	−0.514* (0.01)
F4	−0.401* (0.047)	−0.339 (0.11)	−0.399* (0.048)	−0.515* (0.01)				

*Correlation is significant at the 0.05 level (two tailed); $With diagnostic subtype as covariate. PANSS – Positive and Negative Syndrome Scale

educational attainment in comparison to controls, which is consistent with previous literature.[36] More patients in SCZ group belonged to lower socioeconomic class than the control group, which is in line with a previous research.[37] In addition, SCZ group had a higher prevalence of psychiatric disorders in the family, which is consistent with an earlier research.[38]

Sensory gating was significantly lower at F3 and F4 sites in SCZ group. This implies that the frontal regions are more sensitive to deficient sensory gating in SCZ. Although previous research has consistently shown gating deficits in SCZ group at Cz site,[10,15-21] there have been a few reports which failed to demonstrate differences in gating between SCZ patients and NCs.[39-42] Some researchers have explained that methodological differences (patient positioning, click intensity, click duration, and patient attention during the test) may have influenced their results. As we employed the widely used ERP parameters, methodological issues may not be sufficient to explain our findings. Another study inferred that their sample consisted of young patients and that gating may be age dependent.[42] However, the mean age of our sample was higher and age could not have influenced the results. Boutros *et al*.[43] and Johannesen *et al*.[44] had noted that patients with paranoid SCZ did not demonstrate gating deficits compared to controls, whereas disorganized/undifferentiated subtype demonstrated deficits. As nearly half of our patient group comprised of the paranoid subtype, it may have influenced the results. However, when the diagnostic subtype was used as a covariate to sensory gating correlations, it did not consistently influence the findings. Broadly, we may suggest the use of frontal sites to assess sensory gating apart from the conventional vertex site.

Patients with SCZ had lower S1 amplitude at F3 and F4, which may reflect lower sensitivity to novel sound stimuli and have a lower degree of reactivity in SCZ as described by previous investigators.[19] Moreover, it was observed that, in comparison to the control group, the S2 amplitude did not differ significantly. This is similar to some previous findings by researchers who concluded that the differences in P50 gating between the two groups were driven by abnormalities in S1 but not in

S2. Johannesen *et al*.[44] and Brenner *et al*.[45] noticed an abnormally small S1 response, in the presence of a normal S2 response, among patients with SCZ. In contrast, other investigators reported that index of sensory gating is independent of S1 amplitude.[46,47] Conventional studies by Freedman *et al*.[10,11,13-16] indicated that poor sensory gating is a result of a lack of gating out of the testing or second stimulus.

Thus, the gating deficits in our sample were driven by an abnormally low S1 rather than an inability to suppress S2. Our findings are in contrast with the long-held view that SCZ is associated with a suppression deficit.

The brain structures mediating sensory gating in the auditory system have been well studied. Freedman *et al*., in their research on animals, had strongly indicated the hippocampus as a principal mediator of sensory gating.[48] However, Boutros and Belger inferred that sensory gating is a process with various steps mediated by different brain areas at different stages.[49] Early, preattentive stages may involve filtering out irrelevant input and are mediated by neocortical (prefrontal and perisylvian) regions, whereas the hippocampus proper contributes more to a later, and possibly attentive, filtering in of relevant input.[49] In addition, patients with damage to the dorsolateral prefrontal cortex show impairment in auditory habituation of P50.[50] Thus, the prefrontal cortex may contribute to regulating the P50 sensory gating effect as part of its general role in the inhibitory control of sensory flow. Moreover, Mayer *et al*. conducted an event-related fMRI study to examine both the cortical and deep neuronal sources that mediate the sensory gating response in a population of healthy controls and concluded that a large network of cortical and subcortical structures, including both the bilateral dorsolateral prefrontal cortex and the auditory cortex, is implicated in auditory sensory gating.[51] There was no evidence of hippocampal involvement in sensory gating in their study.[51] Nagamoto *et al*.[52] had suggested that the vertex site (Cz) was best for recording P50, considering research which indicated hippocampus and other central and deep structures to be the origin of P50. In view of the recent research which implicates the role of prefrontal cortex and auditory cortex as neural generators of P50, we suggest that sensory gating should be assessed at other sites in addition to the vertex, particularly the frontal areas that were found in our study to show specificity to sensory gating deficits. Further, based on our study results, we suggest that the sensory gating deficits found in SCZ patients specifically represent deficits in early, preattentive processes.

We were able to demonstrate a cross-sectional relationship between abnormal sensory gating and psychopathology. Our findings suggest that sensory gating worsened with an increase in the severity of positive psychotic symptoms as measured by PANSS. Potter *et al*.[53] reviewed the existing literature to explore the clinical correlates of enhanced P50 gating but concluded that a majority of studies failed to find a relationship between P50 and global measures of clinical severity like PANSS. Our novel findings support the explanatory model which hypothesizes that abnormal response to sensory input could be a cause of symptoms in SCZ, especially positive.

Strengths and limitations

Existing literature has shown that atypical antipsychotics can normalize gating deficits in SCZ,[54-57] and many studies evaluating sensory gating in SCZ have included patients on neuroleptics.[22] However, the confounding effect of antipsychotics on gating was absent in our study, as patients with SCZ were drug naïve or drug free. In addition, patients in our sample were not using nicotine in any form as it can influence sensory gating in patients with SCZ.[58] However, our study has its limitations as it was of cross-sectional design. Research has shown that level of attention to the clicks can influence gating,[59] but our patients were not on medications and were symptomatic, which made it difficult to ascertain whether they were paying attention to the clicks. In addition, we specifically did not assess whether patients in the patient group were actively hallucinating or not. Not controlling for this factor might confound the generalizability of the findings as it has been found that sensory gating significantly differs between auditory hallucinations "on" and "off" states.[60]

Statistical limitations

Limited sample size, which restricts the generalizability of the results, is an important limitation of the study. Moreover, the issue of multiple comparisons, which is inherent to brain topographical neurophysiological studies, is a constraint. When controlling for multitesting, statistical differences were found to lose significance, especially in the fronto-central and central regions. However, while it controls false positives, this kind of correction has been argued to increase the probability of producing false negatives that reduce the statistical power of the study.

CONCLUSIONS

Our study reiterates sensory gating abnormalities in SCZ, but these deficits were apparent specifically at frontal sites. A smaller S1–S2 measure in patients with SCZ was driven predominantly by an abnormally small S1 rather than an inability to suppress S2, which is in contrast with the long-held view of suppression deficits in SCZ. Our study also demonstrated a correlation between sensory gating and measures of

psychopathology, which strengthens the hypothesis that abnormal response to sensory input may contribute to the symptoms of SCZ.

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Conflicts of interest
There are no conflicts of interest.

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SUPPLEMENTARY TABLES

Supplementary Table S1: Comparison of mean S1 amplitudes of schizophrenia and control groups

Variable	Schizophrenia		*n*	Control		*n*	*Z*	*P*
	Mean±SD	Mean rank		Mean±SD	Mean rank			
F3	1.25±1.22	16.45	21	3.74±2.65	29.42	25	−3.264	0.001**,#
FZ	1.34±1.22	13.68	14	3.22±2.18	23.54	25	−2.591	0.010**
F4	1.42±1.23	14.75	20	3.79±2.25	29.60	25	−3.769	<0.001**,#
FC3	1.04±0.82	17.87	19	2.09±1.63	26.02	25	−2.086	0.037*
FCZ	0.81±0.61	18.96	23	1.81±1.43	29.60	25	−2.632	0.008*
FC4	1.24±0.92	18.00	19	2.48±2.01	25.92	25	−2.026	0.043*
C3	1.00±0.59	23.40	20	1.06±0.89	22.68	25	−0.183	0.855
CZ	0.87±0.74	19.02	21	1.62±1.31	27.26	25	−2.073	0.038*
C4	0.97±0.84	20.95	21	1.67±1.84	25.64	25	−1.180	0.238
CP3	1.08±0.65	26.74	23	1.00±0.83	22.44	25	−1.063	0.288
CPZ	0.89±0.52	25.55	21	0.82±0.74	21.78	25	−0.948	0.343
CP4	1.25±1.24	20.40	20	1.73±1.67	25.08	25	−1.188	0.235
P3	1.81±1.08	24.15	20	1.85±1.67	22.08	25	−0.525	0.599
P4	1.93±1.55	20.40	20	2.42±1.80	25.08	25	−1.188	0.235
PZ	1.41±0.93	27.18	20	0.95±0.87	19.66	25	−1.908	0.056

Mann–Whitney test was used to test the differences between schizophrenia and control groups. *Statistically significant at the 0.05 level (two tailed); **Statistically significant at the 0.01 level (two tailed); #Statistically significant at the 0.0033 level (Bonferroni correction for multiple comparisons). SD – Standard deviation

Supplementary Table S2: Comparison of mean S2 amplitudes of schizophrenia and control groups

Variable	Schizophrenia		*n*	Control		*n*	*Z*	*P*
	Mean±SD	Mean rank		Mean±SD	Mean rank			
F3	1.36±0.71	19.75	18	1.81±1.61	21.11	22	−0.367	0.714
FZ	1.35±0.61	15.33	12	1.84±1.31	17.95	21	−0.749	0.454
F4	1.68±0.61	18.18	17	1.96±1.11	20.57	21	−0.661	0.509
FC3	0.97±0.49	19.83	18	1.32±1.33	18.21	19	−0.456	0.648
FCZ	0.93±0.54	16.29	14	1.31±1.23	18.35	20	−0.595	0.552
FC4	1.07±0.70	17.32	17	1.31±0.84	20.43	20	−0.869	0.385
C3	0.84±0.41	20.13	19	0.89±0.76	18.87	19	−0.350	0.726
CZ	0.62±0.37	16.38	16	1.07±0.91	19.37	19	−0.861	0.389
C4	1.01±0.63	20.32	19	1.02±0.72	19.70	20	−0.169	0.866
CP3	1.07±0.49	23.85	20	1.10±0.85	21.38	24	−0.636	0.524
CPZ	0.55±0.45	14.91	17	0.86±0.57	20.92	18	−1.734	0.083
CP4	1.13±0.97	24.63	23	1.26±1.65	22.37	23	−0.571	0.568
P3	1.72±0.89	23.29	21	1.57±0.98	20.77	22	−0.656	0.512
P4	1.75±1.28	24.42	24	2.08±2.16	25.56	25	−0.280	0.779
PZ	1.32±0.85	27.65	24	1.03±1.05	21.35	24	−1.557	0.119

Mann–Whitney test was used to test the differences between schizophrenia and control groups. SD – Standard deviation

Supplementary Table S3: Comparison of mean S1 latencies of schizophrenia and control groups

Variable	Schizophrenia		*n*	Control		*n*	*Z*	*P*
	Mean±SD	Mean rank		Mean±SD	Mean rank			
F3	65.68±16.73	20.21	21	71.07±25.09	26.26	25	−1.534	0.125
FZ	55.63±61.28	18.79	14	67.01±23.87	20.68	25	−0.50	0.617
F4	65.52±17.91	19.65	20	73.59±18.96	25.68	25	−1.542	0.123
FC3	60.52±16.45	20.79	19	61.86±30.27	23.80	25	−0.772	0.440
FCZ	63.48±14.94	25.70	23	57.72±29.26	23.40	25	−0.569	0.570
FC4	60.01±15.08	17.68	19	71.85±23.85	26.16	25	−2.176	0.030*
C3	60.54±18.81	24.23	20	54.82±31.36	22.02	25	−0.564	0.573
CZ	65.72±15.70	29.17	21	51.74±18.32	18.74	25	−2.628	0.009**
C4	64.56±16.09	21.88	21	65.98±27.46	24.86	25	−0.753	0.452
CP3	66.24±18.76	23.98	23	67.46±20.01	24.98	25	−0.249	0.803
CPZ	67.30±16.85	27.86	21	54.67±20.30	19.84	25	−2.021	0.043*
CP4	70.8±18.14	22.68	20	69.63±23.14	23.26	25	−0.149	0.881
P3	71.62±15.90	21.68	20	73.35±18.42	24.06	25	−0.612	0.541
P4	80.22±11.25	23.63	20	77.10±16.04	22.50	25	−0.289	0.772
PZ	78.07±14.52	24.50	20	70.10±23.44	21.80	25	−0.693	0.489

Mann–Whitney test was used to test the differences between schizophrenia and control groups. *Statistically significant at the 0.05 level (two tailed); **Statistically significant at the 0.01 level (two tailed). SD – Standard deviation

Supplementary Table S4: Comparison of mean S2 latencies of schizophrenia and control groups

Variable	Schizophrenia		*n*	Control		*n*	*Z*	*P*
	Mean±SD	Mean rank		Mean±SD	Mean rank			
F3	60.23±15.13	18.17	18	67.41±18.82	22.41	22	−1.145	0.252
FZ	64.11±14.53	15.42	12	68.00±18.19	17.90	21	−0.713	0.476
F4	67.19±18.94	18.59	17	69.21±18.76	20.24	21	−0.458	0.647
FC3	63.75±15.43	18.78	18	65.20±18.69	19.21	19	−0.122	0.903
FCZ	62.68±17.28	15.29	14	67.77±17.51	18.26	19	−0.876	0.381
FC4	61.11±14.08	19.15	17	62.84±19.08	18.88	20	−0.076	0.939
C3	63.86±15.84	19.05	19	64.79±18.07	19.95	19	−0.249	0.803
CZ	61.48±16.44	18.66	16	62.27±19.76	17.45	19	−0.348	0.728
C4	65.51±16.57	21.61	19	62.45±19.61	18.48	20	−0.859	0.391
CP3	69.57±16.44	24.63	20	63.50±18.49	20.73	24	−1.004	0.316
CPZ	70.99±13.40	17.56	17	71.29±19.63	18.42	18	−0.249	0.803
CP4	70.15±17.49	24.91	23	65.39±17.39	22.09	23	−0.715	0.475
P3	76.14±13.70	27.86	21	60.58±13.46	16.41	22	−2.991	0.003**,#
P4	76.96±14.80	29.23	24	67.96±13.90	20.94	25	−2.033	0.042*
PZ	76.15±15.35	27.25	24	69.27±15.41	21.75	24	−1.364	0.172

Mann–Whitney test was used to test the differences between schizophrenia and control groups. *Statistically significant at the 0.05 level (two tailed); **Statistically significant at the 0.01 level (two tailed); #Statistically significant at the 0.0033 level (Bonferroni correction for multiple comparisons). SD – Standard deviation