



## Research Paper

# Different P50 sensory gating measures reflect different cognitive dysfunctions in schizophrenia



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## ABSTRACT

The P50 is an early component of auditory evoked potentials and a measure of sensory gating deficits. This evoked potential component is thought to be an important endophenotype candidate for schizophrenia. Recent research suggests that instead of the P50 ratio, S1 and S2 amplitudes should be evaluated for sensory gating. However, no studies have focused on the relationship between cognitive dysfunction and P50 sensory gating deficits using S1 and S2 amplitudes. The purpose of the present study was to investigate the association between the P50 ratio (S2/S1), S1 and S2 amplitudes, and neuropsychological cognitive domains using stepwise multiple linear regression analyses. Results demonstrated a significant relationship between executive functioning and the P50 ratio and between sustained attention and S2 amplitude, respectively. Our findings suggest that the P50 ratio and S2 amplitude reflect distinct neurophysiological substrates associated with different cognitive functions.

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## 1. Introduction

Perceptual and cognitive deficits are apparent in schizophrenia. Neuropsychological tests, neuroimaging, and event-related brain potentials (ERPs) are popularly used to assess for these deficits. The P50 is an early component of auditory evoked potentials. The P50 response amplitude of the second (S2) or test stimulus [to that of the first (S1) or conditioned stimulus] demonstrates sensory gating. Deficits in sensory gating are an important endophenotype candidate for schizophrenia (Braff and Light, 2005; Turetsky et al., 2007). Although several previous studies have investigated associations between the P50 ratio and clinical symptoms, researchers have not confirmed a cross-sectional or longitudinal relationship between P50 sensory gating and specific clinical symptoms (Potter et al., 2006).

Several studies have investigated the relationship between P50 sensory gating and cognitive dysfunction. Erwin et al. (1998) divided patients into high- and low-P50 abnormality groups and compared neuropsychological performance of these two groups. The high-P50 abnormality group showed greater deficits in attention profile scores compared to performance on other neuropsychological measures. Cullum et al. (1993) compared patients with schizophrenia and control subjects with respect to P50 sensory gating and memory and attention and found P50 abnormalities as well as deficits in sustained attention in the patients.

Sanchez-Morla et al. (2013) evaluated P50 sensory gating between 160 patients with schizophrenia and 64 normal controls. The authors

did not observe a significant association between the P50 ratio and the neuropsychological tests they employed. Using magnetoencephalography (MEG), Thoma et al. (2003) showed that compared to control subjects, patients with schizophrenia have sensory gating abnormalities reflected by the M50 (which corresponds to the P50 component) and significant correlations between the M50 and sustained attention and working memory. Although these small-sample studies indicate that P50 (or M50) sensory gating might be associated specifically with attention and memory, among the various cognitive domains impaired in schizophrenia, a large-sample study by Sanchez-Morla et al. (2013) observed no association between the P50 ratio and cognitive functioning. Therefore, no clear association between P50 sensory gating and cognitive dysfunction has been established.

Recent research has proposed that rather than the P50 ratio, S1 and S2 amplitudes should be evaluated in terms of sensory gating. Indeed, a meta-analysis assessing the P50 ratio (S2/S1) and S1 and S2 amplitudes in schizophrenia revealed that overall effect sizes for the P50 ratio, S1 amplitude, and S2 amplitude were 0.93 (large), 0.19 (small), and 0.65 (medium to large), respectively (Chang et al., 2011). Since the S2 amplitude effect is medium to large, some authors argue in favor of increasing the importance of this amplitude with regard to schizophrenia. For example, Shan et al. (2010) assessed P50 sensory gating among 81 patients with schizophrenia and 47 normal controls, reporting that S2 amplitudes were larger among the patients compared to normal controls. Conversely, Jansen et al. (2010) measured P50 sensory gating among 25 patients with schizophrenia and 25 normal controls and demonstrated a significant S1 amplitude reduction among the patients. These findings suggest that S1 and S2 amplitudes are sensitive to sensory gating and suitable for quantitative analysis. However, the three aforementioned ERP studies, which

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examined the association between P50 sensory gating and cognitive functioning, only assessed the P50 ratio.

The purpose of the present study was to investigate the association between the P50 ratio (S2/S1), S1 and S2 amplitudes, and neuropsychological cognitive domains using stepwise multiple linear regression analyses. While, P50 sensory gating is less affected by first- and second-generation antipsychotic drugs (Adler et al., 2004; Su et al., 2012), clozapine and high-dose quetiapine tend to improve abnormal P50 sensory gating among patients with schizophrenia (Adler et al., 2004; Oranje et al., 2013). Thus, the present study recruited patients with schizophrenia who were administered second-generation antipsychotic drugs, with the exception of clozapine and high-dose quetiapine.

## 2. Methods

### 2.1. Participants

Forty-one (16 females, 25 males) schizophrenic patients who met DSM-IV criteria were assessed with electrophysiological measurements and neuropsychological tests. Patients' mean age was 29.3 years (SD = 7.8 years). The mean duration of illness was 5.4 years (SD = 5.9). Patients were taking the following second-generation antipsychotic drugs at the time of testing: aripiprazole (n = 5, mean CPZ equivalent dose  $\pm$  SD, 345.0  $\pm$  257.6 mg/day), blonanserin (n = 1, CPZ equivalent dose, 300.0 mg/day), olanzapine (n = 7, mean CPZ equivalent dose  $\pm$  SD, 685.7  $\pm$  323.7 mg/day), perospirone (n = 8, mean CPZ equivalent dose  $\pm$  SD, 301.4  $\pm$  243.0 mg/day), quetiapine (n = 12, mean CPZ equivalent dose  $\pm$  SD, 556.2  $\pm$  438.5 mg/day), or risperidone (n = 13, mean CPZ equivalent dose  $\pm$  SD, 407.7  $\pm$  262.9 mg/day). Some patients were taking anticholinergic agent, Biperiden (n = 10, mean dose  $\pm$  SD, 3.2  $\pm$  1.7 mg/day), antidepressants (n = 9, mean imipramine equivalent dose  $\pm$  SD, 113.9  $\pm$  75.1 mg/day). Thirty-four patients were taking anxiolytics (mean diazepam equivalent dose  $\pm$  SD, 30.9  $\pm$  37.0 mg/day). Clinical symptoms were assessed with the Positive and Negative Syndrome Scale (Kay et al., 1987). The mean values for positive, negative, and general psychopathology scale score were 20.4 (SD = 7.1), 20.6 (SD = 7.7), and 42.1 (SD = 24.6), respectively. The local ethics committee from Hokkaido University approved this study. After a complete study explanation, subjects provided written informed consent.

### 2.2. EEG recording and analysis

Electroencephalogram (EEG; bandpass 0.16–30 Hz, digitized at 500 Hz) recording was obtained from Fz, Cz, and Pz electrodes according to the international 10/20 system. Ag/AgCl electrodes were used, and impedance was kept below 10 k $\Omega$ . All electrodes were referenced to the earlobes. Electro-oculogram (EOG) recording was gathered from electrodes lateral to and below the left eye. The paired-click paradigm was performed to elicit the P50 component. A pure tone (1500 Hz, 6-ms duration, 80 dB SPL) was used as the click sound and presented during a 500-ms interval through a loudspeaker. The interval between paired stimuli was 8 seconds. The signals were digitized for an epoch of 400 ms starting 200 ms prior to the presentation of each auditory stimulus. Individual trials were rejected when EEG voltage was greater than  $\pm$  35  $\mu$ V, indicative of excessive muscle activity, eye movements, or other artifacts. We defined the P50 component as the most positive peak between 30 and 70 ms post-stimulus onset. We measured the peak-to-peak P50 amplitude from a preceding negative trough to the positive peak. This was done because the baseline prior to the second stimulus onset often fluctuated based on the ERP from the first stimulus; the baseline-to-peak P50 amplitude was not appropriate for assessment. The P50 ratio was calculated as the test stimulus response divided by the

**Table 1**

Neurophysiological and neurocognitive measures in patients with schizophrenia.

	Mean (SD)
<i>Neurophysiological measures</i>	
S1 amplitude	1.22 (0.57)
S2 amplitude	0.83 (0.61)
P50 ratio	0.78 (0.62)
<i>Neurocognitive measures</i>	
WCST CA	4.3 (1.6)
WCST PEM	3.1 (5.1)
WCST PEN	5.1 (5.7)
CPT errors	3.8 (5.2)
CPT reaction time	416.6 (76.0)
WFT sums	28.6 (10.1)
Stroop errors	0.8 (1.2)
Stroop RT differences	8.3 (4.6)
TMT-A	92.6 (29.3)
TMT-B	113.2 (43.3)
TMT RT differences	20.6 (35.5)
AVLT immediate	5.2 (1.2)
AVLT delay	6.3 (2.1)

For abbreviation of neuropsychological tests see Section 2.

conditioning stimulus response. We presented the paired stimulus 300 times, which provided 40 minutes of EEG measurement. In consideration of participant load and ear comfort that could influence EEG measurement, we instructed participants to watch a silent film and presented auditory stimuli from a loudspeaker as mentioned above.

### 2.3. Neuropsychological assessment

A battery of neuropsychological tests was administered to all patients. The neuropsychological tests used, and related cognitive domain, were as follows: Wisconsin Card Sorting Test (WCST), executive function; Word Fluency Test (WFT), verbal fluency; Continuous Performance Test (CPT), sustained attention and motor speed; Trail Making Test (TMT), visual-motor processing and motor speed; Auditory Verbal Learning Test (AVLT), verbal learning and immediate and recent memory; and Stroop Test, selective attention. For the WCST, a computerized Japanese Keio University version was used. We assessed category of achievement (CA) and two types of perseverative errors (Nelson and Milner perseverative errors). The CPT was a computerized A-X CPT test administered for approximately 8 minutes. Several characters were presented on the center of a monitor, and subjects were instructed to respond with an "X" after "A" was presented, as soon as possible. The target stimulus was presented 70 times. Each stimulus was presented for 100 ms, and the inter-stimulus interval varied from 1500 to 2000 ms. We assessed both the number of errors and reaction time (RT). The TMT was administered based on a standard procedure, which consists of the TMT-A and TMT-B (Shum et al., 1990). We measured the amount of time required to complete the TMT-A and TMT-B, respectively, and assessed the time to completion between the two (TMT-B minus TMT-A). The WFT was administered from a Japanese version that

**Table 2**

Stepwise multiple regression analysis showing the factors most closely associated with P50 sensory gating.

Independent variables	Dependent variables							
	P50 ratio				S2 amplitude			
	R	R <sup>2</sup>	SE	P	R	R <sup>2</sup>	SE	P
WCST PEN	0.434	0.188	60.397	0.013	–	–	–	–
CPT reaction time	–	–	–	–	0.456	0.208	0.464	0.009

instructed patients to produce as many words as possible initiated from each of three Japanese, cursive syllables (“si,” “i,” and “re”) for 1 minute. We counted the total number of produced words across the three conditions. The Stroop test used was a Japanese version consisting of two figures on A4 sized paper. The former had 24 circles painted with red, blue, yellow, and green ink. The patients were instructed to read aloud the color name (congruent condition). The latter condition consisted of 24 Chinese characters indicating one of the above four colors, but each character was painted in a different color from its meaning. Patients had to read the color name rather than the characters (incongruent condition). We counted the number of errors in the incongruent condition and assessed RT differences between the two conditions (incongruent minus congruent). The AVLT was developed using a normed procedure to measure both immediate memory and recent memory. We orally presented 10, commonly used Japanese words 5 times. The patients, during each trial, were instructed to recall as many of the words as possible. Patients completed the 4th recall session after 30 minutes and then were asked to recall the full list for the 5th recall session. We counted the number of recalled words across the 5 sessions. We regarded the 1st recall session as “immediate memory” and the 5th recall as “recent memory.”

#### 2.4. Statistical analysis

In order to assess relationships between cognitive domains and P50 sensory gating, several stepwise regressions were performed on the neuropsychological tests, P50 ratio, and S1 and S2 amplitudes. Independent variables were the P50 ratio and S1 and S2 amplitudes, and the predicted variables were as follows: WCST CA (category of achievement); WCST PEM (Milner perseverative errors); WCST PEN (Nelson perseverative errors); CPT errors, CPT RT, and WFT sums; Stroop errors; Stroop RT differences; TMT-A, TMT-B, and TMT RT differences; AVLT immediate; AVLT delay.

### 3. Results

Table 1 shows neurophysiological measures (S1 and S2 amplitude, P50 ratio) and neurocognitive measures. A stepwise multiple regression analysis using the P50 ratio as the dependent variable demonstrated that more Nelson perseverative errors during the WCST (WCST PEN) were associated with an increased P50 ratio ( $p < .05$ ). A second analysis using S1 amplitude as the dependent variable did not find any significant relationships. However, an analysis using S2 amplitude as the dependent variable revealed that longer RTs during the CPT (CPT RT) were associated with an increase in S2 amplitude ( $p < .001$ ).

Generally, the P50 ratio and S2 amplitude appear to be higher among schizophrenic patients as compared to normal, control subjects. Our findings suggest that an increased P50 ratio or S2 amplitude is associated with cognitive deficits. Table 2 shows results from our stepwise multiple regression models.

### 4. Discussion

The purpose of the present study was to investigate associations between P50 sensory gating (P50 ratio, S1 and S2 amplitudes) and neuropsychological functioning. The P50 ratio and S1 and S2 amplitudes were used as dependent variables for a series of multiple regression analyses. We observed associations between executive functioning (WCST PEN) and the P50 ratio and between sustained attention (CPT RT) and S2 amplitude, respectively.

Interestingly, it appears the P50 ratio and S2 amplitude might reflect different cognitive domains. These results are somewhat different from those previously reported. For instance, previous

studies have typically just focused on the P50 ratio. Two studies demonstrated an association between attention and the P50 ratio (Cullum et al., 1993; Erwin et al., 1998), while one large-scale study revealed no significant association between the P50 ratio and neuropsychological functioning (Sanchez-Morla et al., 2013). The two studies observing associations between the P50 ratio and attention did not measure executive functioning per se, but Sanchez-Morla and Santos utilized Wisconsin Card Sorting Test performance, one of the tests used in the present study. Our results regarding the association between the P50 ratio and executive functioning was different from these previous studies in two ways. Firstly, we did not find any significant relationships between the P50 ratio and any attention domain. Cullum et al. (1993) did not use the CPT or any other measure assessing RT. Erwin et al. (1998) did use the CPT, which was a bit different from that used in our study, but did not calculate RT. Thus, neither study measured RT during sustained attention; thus, differences in attentional measures among studies might contribute to the observed inconsistencies. Secondly, a significant association between Nelson perseverative errors during the WCST was observed in our study. Sanchez-Morla et al. (2013) converted raw scores to a T-score distribution in terms of the number and type of perseverative WCST errors. The present study utilized raw Nelson and Milner perseverative error scores. However, we assumed these differences likely would not be critical to the inconsistencies between studies; nevertheless, further study is needed to better determine the disparate findings observed.

Another intriguing observation was that CPT RT predicted increases in S2 amplitude. Although some previous studies demonstrated that S2 amplitude itself was higher among schizophrenia patients compared to normal controls (Shan et al., 2010, 2013), no studies had previously investigated relationships between cognitive performances and S2 amplitude. It is not surprising that neurophysiological processing related to the S2 response would differ from the P50 ratio. Thus, the P50 response relating to S2 might be suppressed by an auditory sensory representation of S1. Therefore, encoding processes (e.g., sensory registration) could be substantially reduced. These S2-specific neural processes provided contributions through activation of GABAergic interneurons via cholinergic inputs in the hippocampus (Vlcek et al., 2014). The S2 response is sensitive to evaluative processes, especially when encoding information is related to preceding information. From here, we can argue that the S2 response shares common processes with RT performance during the CPT.

### 5. Conclusions

Based on the present findings, it appears that the P50 ratio and S2 amplitude reflect distinct neurophysiological substrates, revealing differential associations with higher cognitive functions. Although the P50 ratio is one of the more important endophenotype candidates for schizophrenia (Braff and Light, 2005; Turetsky et al., 2007), the present study suggests that focusing on multidirectional measures of P50 abnormality (i.e., S1 and S2 amplitudes) is important to further explore cognitive aspects related to sensory gating dysfunction in schizophrenia.

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