Is P50 Suppression a Measure of Sensory Gating in Schizophrenia?

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Background: *Abnormal P50 response has been hypothesized to reflect the sensory gating deficit in schizophrenia. Despite the extensive literature concerning the sensory filtering or gating deficit in schizophrenia, no evidence has been provided to test the relationship of the P50 phenomenon with patients' experiences of perceptual anomalies.*

Methods: *Sixteen drug-free DSM-IV diagnosed schizophrenic patients who reported moderate to severe perceptual anomalies in the auditory or visual modality were examined as compared to 16 schizophrenic patients who did not report perceptual anomalies, and 16 normal subjects. Both control groups were age- and gender-matched with the study group.*

Results: *Patients reporting perceptual anomalies exhibited P50 patterns that did not differ from normal subjects. In contrast, patients who did not report perceptual anomalies showed the abnormal P50 ratios previously found to be associated with schizophrenia.*

Conclusions: *These paradoxical findings do not support the hypothetical relationship between the P50 and behavioral measures of sensory gating, suggesting that additional studies are needed to further explore the clinical correlates of the P50.* Biol Psychiatry 1998;43: 873–878

Key Words: Schizophrenia, sensory gating, P50, perceptual anomaly

Introduction

Patients with schizophrenia have difficulty in processing sequentially presented sensory stimuli (Adler et al 1982; Freedman et al 1983; Nuechtertlein and Dawson 1985; Braff et al 1995; Shagass 1977). Historically, an inability to properly filter sensory inputs has been hypothesized to contribute to abnormalities of perception and attention observed in schizophrenia (Venables 1964). Based upon a series of studies of perceptual errors made by schizophrenic persons in judgments of size constancy, Weckowicz and Blewett (1959) suggested that accurate perception requires a sensory filter that allows the perceiver to attend selectively to certain external stimuli while disregarding irrelevant stimuli. In contrast to normal persons, a subgroup of schizophrenic patients were unable to filter out irrelevant stimuli, resulting in perceptual abnormalities. Weckowicz and Blewett reasoned that the cognitive defects observed in schizophrenia were secondary to the impairment of the sensory filter. In their classic paper, McGhie and Chapman (1961) described clinical observations of 26 schizophrenic cases as support for the theory of abnormal filtering of sensory input in schizophrenia. They observed that patients with schizophrenia had difficulty concentrating, decreased ability to focus on external sensory stimuli, and a hyperawareness of background noises. The heightened sensory vividness of irrelevant stimuli reported by schizophrenic persons was theorized to be due to a breakdown in selective sensory inhibitory function, resulting in the flooding of an undifferentiated mass of sensory input into consciousness. Venables' early work (Venables 1964) also provided evidence that abnormal arousal coupled with an inability to restrict the range of attention in acute schizophrenics caused a flooding of sensory impressions.

Hetrick et al (1995) reported a similar result that more than 50% of hospitalized schizophrenic patients had experienced severe perceptual anomalies, primarily in auditory and visual modalities. These findings are consistent with hypersensitivity to external stimuli as a phenomenological characteristic of schizophrenia. Recent data from neural imaging studies (Andreasen et al 1994; Buchsbaum et al 1996) have supported the concept of a sensory filtering deficit in schizophrenia by demonstrating that the lesions of thalamus, which are proposed to mediate atten-

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tion and information processing, might play an important role in schizophrenia.

The biological mechanism of the defective sensory filtering in schizophrenia has been proposed by Freedman and colleagues (Freedman et al 1983, 1987; Adler et al 1982, 1985, 1988; Siegel et al 1984; Baker et al 1987, 1990; Nagamoto et al 1989). They adopted a physiological test (Eccles 1969) to assess sensory gating function using auditory evoked potentials. In a dual-click (S1–S2) auditory P50 paradigm, it was found that, in normal subjects, the amplitude of P50 to S2 was reduced by more than 50% compared to the S1 response. This relative suppression of response to the second click (S2) was interpreted as evidence of auditory sensory gating, in which the first stimulus (S1) activates an inhibitory system, reducing the amplitude of the response to S2 (Adler et al 1982). In contrast to normal subjects, schizophrenic patients are reported often to show an S2/S1 ratio of greater than 80%, indicating impaired sensory gating (Adler et al 1982; Freedman et al 1983, 1987; Nagamoto et al 1989). This increased S2/S1 ratio has been proposed as a biological marker (Freedman et al 1983) of a fixed (Waldo and Freedman 1986) and genetic trait (Waldo et al 1991) in schizophrenia and suggested to reflect the primary sensory deficit of the disease process (Freedman et al 1987). Following a description of the filtering theory of schizophrenia of McGhie and Chapman (1961) and a review of their own studies, Freedman and colleagues (Freedman et al 1987; Waldo et al 1991) concluded that the deficit in P50 sensory gating might reflect a neuronal substrate of the inability to filter sensory information in schizophrenia. This important conceptualization has provided an impetus for other P50 investigations that have, for example, compared different diagnostic groups (Franks et al 1983), described gender effects (Hetrick et al 1996), and studied the influence of attention distraction in normal subjects (Jin and Potkin 1996).

Despite the extensive literature concerning the sensory filtering or gating deficit in schizophrenia, no evidence has been provided that tested the relationship of the P50 phenomenon with patients' experiences of hypersensitivity to external stimuli. The goal of this study was to use the paired click sensory gating paradigm to measure the P50 responses in schizophrenic patients who report experiences of severe perceptual difficulties similar to those described by McGhie and Chapman (1961), and compare the P50 responses of these patients with patients and normal controls who do not report experiencing sensory anomalies. If the P50 ratio reflects the sensory filtering deficits hypothesized to characterize schizophrenia, a positive relationship between patients' perceptual anomaly experiences and the auditory evoked potential measures should be revealed.

Methods and Materials

Subjects

Based on structured interviews of consecutive admissions, 16 drug-free (washout period: 1–3 weeks) DSM-IV diagnosed schizophrenic patients (4 women and 12 men; mean age: 37.6 ± 2.1 years) who reported difficulties involving processing perceptual information were hospitalized and included in this study. During the structured interview subjects were asked whether they had experienced perceptual disturbance in the week preceding and including the day of the interview in either visual or auditory modalities according to the following six items: 1) real sounds seem more intense or loud; 2) feelings of being flooded/inundated by real sounds; 3) cannot focus attention on one real sound or voice to the exclusion of others; 4) real sights or colors seem unusually intense; 5) feelings of being flooded/inundated by sights or colors; and 6) cannot focus attention on one visual perception to the exclusion of others. A distinction was made between responses to "real," external stimuli versus imagined, internally derived stimuli (i.e., hallucinations). The 16 hospitalized patients who reported positively on one or more of these items more than half the time on a five-point scale ("never," "rarely," "half the time," "often," and "always") were included in the perceptual anomaly group. The structured interview for the assessment of perceptual anomalies took between 15 and 30 min to complete. Table 1 lists examples of patients' reported experiences. Another 16 hospitalized patients who did not report perceptual anomalies during the interview (or who reported anomalies less than 20% of the time) and 16 normal controls (also given the interview) were matched with the perceptual anomaly group based on age and gender. The patients' clinical severity of illness was assessed by Brief Psychiatric Rating Scale (BPRS) total score. The perceptual anomaly group had a slightly higher BPRS rating (38.3 ± 18.9) than the intact perception group (30.7 ± 15.5), but the difference was not statistically significant ($t = 1.02$, $p > .1$). There was no significant difference of clinical subtype distribution (perceptual anomaly group: 11 paranoid, 5 nonparanoid; intact group: 7 paranoid, 9 nonparanoid. $\chi^2 = 1.14$, $p > .1$) or duration of illness (perceptual anomaly group: 9.4 ± 11.2 years; intact group: 11.1 ± 9.7 years. $t = 0.69$, $p > .1$) between the two groups.

P50 Procedure

During the test, subjects were supine on an adjustable testing bed in a dark room. They were instructed to relax with their eyes closed. A series of paired clicks (S1 and S2) separated by 500 msec were presented at 10-sec interpair intervals through a set of headphones. Clicks were produced by rectangular pulses of 50-μsec duration and amplified to reach the intensity of 100 dB SPL (Baker et al 1987; Kathmann and Engel 1990).

Evoked potential signals were collected from Ag–Ag C1 cup electrodes placed using adhesive paste at the vertex (Cz) and referenced to linked mastoids. Forty 180-msec electroencephalographic (EEG) epochs, band-pass filtered at 0.56–500 Hz, were sampled by a 16-bit analog-to-digital converter at the rate of 2756 point/sec for each trial. Electro-oculographic (EOG) data

Table 1. P50 Values and Quotes from Patients Subgroup Who Experienced External Sensory Anomalies

Patients #	Quotes	S1	S2	S2/S
1	"When I am talking to someone and I hear other sounds, they all mix together and I lose the whole thing . . . "	8.9	3.4	0.38
2	"I couldn't understand what people were saying, all the noise would get in the way . . . I have too much peripheral vision, things in the side of my eye were too much."	3.4	1.2	0.35
3	"When more than one person was talking, all the words would come together into one sentence and I couldn't understand. There was always too much going on and I couldn't make any sense out of it."	5.0	1.6	0.32
4	"Noises distract my thoughts, so I like to stay in quiet places . . . When people around me are talking, I can't understand what anyone is saying, it needs to be quiet so I can understand."	2.3	1.9	0.83
5	"I get confused when I am in a busy place. I react to one thing, then I react to another, the sounds mix together and I get confused. I get out of orientation, I can't put together all the sounds that are coming in . . . I get overwhelmed and confused, all the sounds come in at the same time."	4.0	3.1	0.77
6	"Cars and noises distract my thoughts. It angers me that cars are allowed to be so loud. Cars and noises take my concentration away from the TV or reading or whatever I am doing. The noises mix with the other noises and it's hard to understand. I get distracted by other people's conversations, my mind wants to listen to other people all at the same time . . . People talking, birds, cars, and other sounds are all too loud. My eyes dart around to look at things in the periphery."	3.6	0	0
7	"I have difficulty attending to one voice when in a group of people. TV is loud, other people's conversations are loud, louder than normal since I came to the hospital. All sounds come to me at once. Things in my peripheral vision catch my eye."	5.4	1.0	0.19
8	"Tuning sound of the radio is disturbing, makes my ears ring. I can't concentrate. TV is too loud. My sense of smell is more sensitive now. The cleaning man uses strong chemicals, I want to get a fan to blow it out."	5.6	1.6	0.29
9	"Sometimes I hear too loud. My ears are sensitive. Door, TV, people talking seem loud. I'd rather just plug my ears. I get too distracted, scattered. I can't focus on one conversation, it's overwhelming. I try to get away, but I'm just sensitive to sounds."	5.3	0	0
10	"Sounds like TV feels like it is knocking and keys rattling my brain. I cannot tune out environmental sounds."	3.5	1.2	0.34
11	"I feel like I can hear the traffic loudly. I am really distracted by the TV and noises around me. It is hard to concentrate. Things in peripheral vision catch my eye."	6.8	0	0
12	"People talking too loud. I'm more distractible than other people. It really gets on my nerves. I just want to tell everybody to shut off the noise and the TV."	7.7	2.0	0.26
13	"When TV is on or people are talking, I get up and move away. I can't concentrate when watching TV. I can hear what other people are saying."	5.6	1.4	0.25
14	"Things are much louder than usual right now. I get very dizzy and my hearing gets mixed up. My ears are so full. Others' voices distract me. I can hardly focus."	9.9	3.8	0.38
15	"The fluorescent light is too bright. When it's on I can't watch TV. Whenever I'm out on the street, things get to my eyes."	4.4	0.5	0.11
16	"I try to get away, but I'm sensitive to sounds. Doors clink, people talk loud. I'm easily distracted, I can't focus on one conversation, it's overwhelming. Things in the corner of my eyes often catch my attention. I feel like I see everything at the same time. It makes me feel flooded."	6.7	2.2	0.33

were recorded to help eliminate interference of spontaneous eye movement or potential startle response. Trials contaminated by major artifacts (± 75 μV) were routinely rejected by a threshold filter. These artifact-free epochs were then averaged on-line by a computer (Neurodata, Inc.). The peak of the P50 wave was selected as the most positive averaged deflection within the range of 40–80 msec after click onset (Cardenas et al 1993). The amplitude was defined as the maximal difference between the positive peak and the preceding negative trough. The latency was measured as the time delay to peak onset after the stimulus.

Results

Sixteen study patients reported perceptual anomalies (hereafter called the perceptual anomaly group). Examples of patients' reports of perceptual anomalies and their P50 measures are listed in Table 1. These quotes illustrate characteristics of the type of perceptual abnormalities recorded while conducting the structured interview, and are consistent with those reported by McGie and Chapman

(1961). Additionally, 16 age- and gender-matched schizophrenics who did not report severe or moderate perceptual anomalies were included in the intact perception group as study controls. Some of these intact perception patients reported minor perceptual anomalies on rare occasions, such as during physical exhaustion; however, the quality of these reports were in sharp contrast to those given by patients in the perceptual anomaly group in both severity and frequency. For example, the intact perception group reported such experiences as 1) "The sound of fire crackers on New Years Eve hurt my ears. Not many other sounds hurt my ears. People honking their horns sometimes hurts my ears too." "My vision is good. The only thing that hurts my eyes is looking into the sun. I can't think of anything else that hurts my eyes"; 2) "I was at a concert one time and it was pretty annoying. The music was loud and hurt my ears. Cars sometimes, but mostly some motorcycles when they go, that sound hurts my ears"; and 3) "Down at the beach the Dumpsters smelled like they had a rancid odor; that smell really bothered me. That smell almost made me ill because it was so bad." These statements were similar to those reported in the normal group of 16.

P50 amplitude ratio measures (S2/S1) were normalized by cubic root transformation due to the skewness of the distribution in the perceptual anomaly group. Analysis of variance (ANOVA) showed that the mean S2/S1 ratio was significantly different among the perceptual anomaly, intact perception, and normal control groups ($F = 8.45$, df = 2,45, $p < .01$). Post hoc t tests revealed that the significant differences were located between the intact perception group and normal controls ($t = 3.11$, df = 15, $p = .01$), and between the intact perception group and the perceptual anomaly group ($t = 3.56$, df = 15, $p < .01$). The intact perception group had higher S2/S1 ratios than both the perceptual anomaly and normal control groups. There was no significant difference in S2/S1 ratio between the perceptual anomaly group and the normal controls ($t = 1.85$, df = 15, $p > .05$). P50 amplitude at S1 and S2 for each subject is displayed in Figure 1.

Analyses also showed that the S2/S1 ratio difference among the three study groups was mainly attributed to the initial conditioning (S1) P50 amplitude. The intact perception group had the lowest amplitude ($F = 13.35$, df = 2,45, $p < .01$) compared with the perceptual anomaly group and normal controls. Post hoc t tests showed significant differences in S1 P50 amplitude between the perceptual anomaly group and the intact perception group ($t = 5.56$, df = 15, $p < .001$), and between the intact group and normal controls ($t = 4.57$, df = 15, $p < .001$). There was no significant difference between the perceptual anomaly group and normal controls in S1 amplitude ($t = 1.20$, df = 15, $p > 1.0$). Amplitudes of S2 responses were greater in normals than schizophrenic patients in both the intact perception and the perceptual anomaly groups ($F = 3.45$, df = 2,45, $p < .05$). There were no significant group differences in P50 latencies (S1 latency: perceptual anomaly = 57.4 ± 5.1; intact perception = 55.6 ± 8.4; normal = 58.3 ± 3.6; $F = 1.09$, df = 2,45, $p > .1$. S2 latency: perceptual anomaly = 56.6 ± 6.6; intact perception = 54.7 ± 10.4; normal = 54.0 ± 4.5; $F = 1.17$, df = 2,45, $p > .1$).

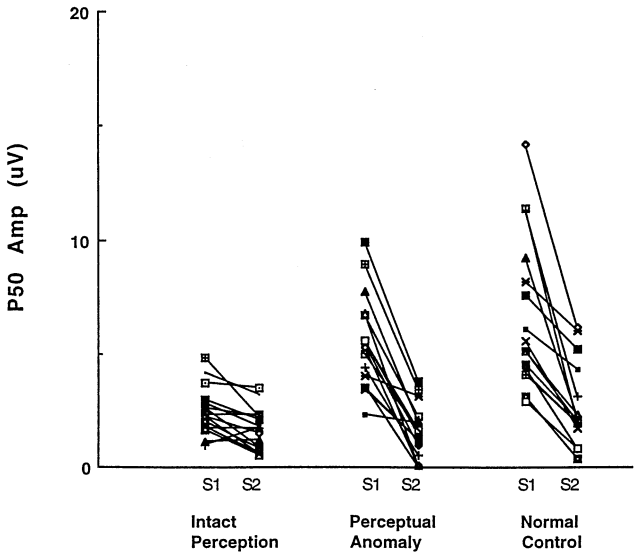

Figure 1. Paired click P50 responses in schizophrenic patients who reported perceptual anomalies, patients who had intact perceptions, and normal controls. The perceptual anomaly group exhibited a P50 pattern nearly identical to the normal group's, while the intact perception group had significantly lower response to the conditioning stimulus (S1) and a greater test-to-conditioning ratio (S2/S1).

Discussion

Contrary to expectations, schizophrenic patients who reported perceptual anomalies exhibited P50 ratios that did not differ from normal controls. Patients who did not experience perceptual anomalies, however, had P50 ratios that were significantly different from normal controls and similar to responses previously observed in groups of schizophrenics (Adler et al 1982; Freedman 1983, 1987; Baker et al 1990). The apparent mismatch between the P50 evoked potential and the reported perceptual experiences observed in the current study suggests that further studies of the behavioral implications of the P50 gating measure are needed.

Consistent with our previous reports (Jin and Potkin 1996; Jin et al 1997), the difference of P50 suppression ratio among the groups was primarily due to the differences in the amplitude of S1 response. Other studies have

found that the amplitude of the P50 response to S1 contributes importantly to differences between schizophrenics and normals in the S2/S1 ratio (Adler et al 1982, 1985, 1988; Freedman et al 1987; Schwartzkopf et al 1993; Cullum et al 1993; Judd et al 1992). We have suggested (Jin et al 1997) that temporal variability in the P50 response to incoming stimuli, possibly also a reflection of a sensory filtering abnormality, may contribute to a diminished P50 amplitude in time-locked averaging. After finding a diminished S1 response in schizophrenic patients, Adler et al (1982) suggested that the constant background discharge of a hyperactive neuronal population may reduce the number of neurons that will respond synchronously to a stimulus, leading to an attenuated response. These results stress the importance of comparing S1 and S2 absolute amplitude measures between groups in addition to S2/S1 ratio, which by itself can mask the relative contribution of each peak.

The intensity of the stimuli applied in the current study was higher than other studies where 70–80-dB SPL clicks were used. It could be argued that the high-intensity stimuli (100 dB) could produce startle responses, which could have influenced the outcome of the study; however, prior studies (Baker et al 1987) that replicated the finding of weak P50 suppression in schizophrenics used an even higher stimulus intensity (110 dB). To minimize the contaminating effect of startle, a threshold filter was used in the recording, including the EOG channel to reject trials exceeding 75 μV. Since the artifacts produced by eyeblinks in the EEG appear as positive deflections (Kathmann and Engel 1990), the S1 P50 amplitude and S2/S1 ratio can be overestimated if blink artifact is present. In this study, however, both amplitude and ratio measures were compatible with those reported in other studies. Additionally, the perceptual anomaly group showed higher S1 amplitude than the intact perception patients, but did not differ in S1 amplitude from the normal group. Therefore, it is unlikely that the lack of P50 suppression in the intact patient group and the relatively normal ratio in the perceptual anomaly group could be caused by startle artifacts.

The sensory filtering deficits hypothesis in schizophrenia proposed by McGhie and Chapman (1961) has been accepted and widely referenced as phenomenological evidence for the recent P50 sensory gating studies (Freedman et al 1987; Geyer et al 1990; Baker et al 1987). To our knowledge, no study has been reported to elucidate the relationship between the clinical phenomenon of perceptual anomalies and the physiological measure of P50. If gating abnormalities in schizophrenia measured by P50 reflect the sensory filtering difficulty described by McGhie and Chapman, then the patients who report sensory anomalies would be expected to show abnormal P50 ratios. Our paradoxical findings that the perceptual anomaly patients demonstrated normal P50 patterns, while those not reporting perceptual anomalies showed the abnormal P50 ratios previously reported to be associated with schizophrenia (Adler et al 1982; Freedman et al 1987), do not support this relationship between the P50 and behavioral measures of sensory gating. These findings may provide an important clue to advance future investigations into the sensory gating phenomenon, although no conclusive statement regarding the normal or abnormal sensory processing mechanisms is warranted by the current study. The present data suggest that additional studies are needed to further explore the behavioral correlates of the P50 (Jin and Potkin 1996; Jin et al 1997) and its relationships with other clinical factors, including the subtype (Boutros et al 1993), length, and severity of illness (Baker et al 1987).

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