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Comparison of four components of sensory gating in schizophrenia and normal subjects: a preliminary report

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Abstract

Dysfunction of sensory gating has been implicated in the pathophysiology of schizophrenia. The goal of this study was to provide evidence that sensory gating dysfunction in schizophrenia patients is a compounded problem with difficulty in filtering out irrelevant input and filtering in relevant input at both an early-preattentive stage and a later, early-attentive stage of information processing. Four components of sensory gating were examined in 12 medicated, stable schizophrenia patients and 12 age- and sex-matched normal control subjects. Evoked potential paradigms designed to examine the effects of stimulus repetition and stimulus change were utilized. Attenuation of the amplitude of the P50 and the N100 evoked potentials with stimulus repetition was significantly decreased in schizophrenia patients as compared to normal control subjects. The presentation of deviant stimuli caused the degree of attenuation to decrease in normal subjects. This effect was much decreased (and at times reversed) in schizophrenia subjects. These data suggest that schizophrenia patients have difficulty inhibiting incoming, irrelevant stimuli and responding to incoming, significant input as measured by preattentive EPs (P50). The data also suggest that similar abnormalities can be demonstrated at a slightly later phase of information processing (i.e. early-attentive phase) using the N100 EP.

Keywords: P50; N100; Evoked potentials; Preattentive sensory gating; Attentive sensory gating

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1. Introduction

The brain appears to possess multiple mechanisms for gating the access of sensory input to higher cortical centers. These gating processes appear to be multicomponent (Boutros et al., 1997) and multiphase (Boutros and Belger, 1999). Dysfunction of sensory gating has been implicated in the pathophysiology of a number of psychiatric disorders (Baker et al., 1987) including schizophrenia (Boutros et al., 1991; Adler et al., 1992). Prior research has tended to focus on preattentive inhibition of irrelevant input (Freedman et al., 1991).

Processing of sensory input seems to require at least two stages: a stimulus identification stage (a stimulus is present) followed by a stimulus evaluation stage. Evidence from the literature suggests that while schizophrenia patients can usually identify the stimuli in their environment, they may have difficulty in evaluating stimulus input (Freedman et al., 1991). Thus, stimulus identification and categorization deficits may result from earlier deficiencies in sensory gating capabilities. Such poor perceptual discrimination of auditory input may contribute to the diminished P300 auditory evoked potential (EP) amplitudes noted in schizophrenia patients (Pfefferbaum et al., 1984).

Sensory gating is commonly measured in EP paradigms. The mid-latency auditory evoked responses (MLAERs) are a series of brain waves that are recorded at the scalp following auditory stimulation (Buchsbaum, 1977). These EPs usually occur between 10 and 250 ms post-stimulation. The MLAERs are known to decrease in amplitude with repetition at short intervals (Fruhstorfer et al., 1986). In a paired click paradigm, the first of a pair of stimuli (S1) is followed by an identical stimulus (S2) a short time later (e.g. 500 ms). The inhibitory capability of the brain is then measured as the ratio of the amplitude of the S2 response to the amplitude of the S1 response (S2/S1). The lower ratios are presumed to reflect better inhibition or better 'gating-out' of irrelevant input.

The broad definition of sensory gating as the ability of the brain to modulate its sensitivity to incoming stimuli (Braff and Geyer, 1990) allows the concept of gating to include both the capacity to attenuate the magnitude of the response to incoming, irrelevant stimuli (gating-out) and to re-respond when a change occurs in ongoing stimuli (gating-in). This broader definition reflects more closely a complex multistage–multicomponent sensory gating concept. A dishabituation effect has been demonstrated in both the P50 MLAER (Boutros et al., 1995a) and in later occurring evoked responses (Boutros and Belger, 1999). Several investigators have reported that deviant stimuli imbedded among a repetitive train of identical tones elicit a negative component between 160 and 200 ms following stimulus onset (Naatanen, 1992) even when the tones are not attended to. It is possible to postulate that both EP amplitude attenuation, due to repetition, and augmentation, due to stimulus change, reflect two distinct components of sensory gating.

We have previously shown that the N100 MLAER can also be reliably used to study sensory gating when examined in paradigms that do not involve attentional manipulations (Smith et al., 1994) and may reflect later occurring sensory gating mechanisms. The P50 sensory gating-indices reflect mainly early preattentional processing (Jerger et al., 1992). Early attempts at examining the possible contribution of the N100 EP to understanding sensory gating were discouraged by a finding of significant test-retest variability (Adler et al., 1982; Freedman et al., 1983). The observation that attentional manipulation can influence the degree of attenuation of the N100 response to S2 stimuli (Guterman et al., 1992) further discouraged the exploration of the N100 as a model for sensory gating. Our N100 test–retest data (Smith et al., 1994) strongly support the need to explore the possible role of the N100 in sensory gating. This conclusion is supported by the earlier finding of Waldo et al. (1988) showing the N100 amplitude deficit to be limited to patients and not to their relatives. Indeed relatives with abnormal P50 gating had N100 amplitudes that were larger than normal, suggesting a compensatory process that is effective in relatives but

fails in patients. Such a compensatory increase in the N100 amplitude has also been reported in healthy subjects who are at an increased risk for developing Alzheimer's disease (Boutros et al., 1995b). N100 amplitude reduction caused by stimulus repetition can be considered, at least to some extent, stimulus-specific. The presentation of a different stimulus following a repeating stimulus often enhances the N100 amplitude (Woods and Elmasian, 1986). This enhancement has been shown to correlate with the magnitude of stimulus change (Butler, 1968; Naatanen, 1985). The available literature, thus, suggests that sensory gating is a multistage operation and that the N100 may be playing a role that is distinct from that reflected by the P50 EP in mediating sensory gating.

We have recently shown that evoked potential paradigms can be developed to examine habituation and dishabituation of both the P50 and the N100 EPs (Boutros and Belger, 1999). In a limited pilot study, we compared the P50 responses of schizophrenia patients and normal control subjects utilizing paired click habituation and dishabituation paradigms (Boutros and Tueting, 1996). As expected, the degree of attenuation of the S2 response was decreased in schizophrenia patients when identical clicks were used to examine habituation. Normal volunteers reacted to the S2 stimuli in the non-identical-pair paradigm with decreased attenuation of S2 responses. Schizophrenia patients, on the other hand, significantly attenuated the amplitudes of their S2 responses when a deviant S2 was presented. The pilot data suggest that the two groups responded fundamentally differently to the identical and non-identical paradigms.

In the current study, we attempt to replicate and extend our prior findings by providing evidence that sensory gating dysfunction in schizophrenia patients is a compounded problem with deficits in four aspects of the sensory gating process. Namely, schizophrenia patients have difficulty in filtering out irrelevant input and filtering in relevant input at both an early preattentive stage (P50) and a later early-attentive stage (N100).

2. Methods

2.1. Subjects

Twelve medicated and stable outpatient schizophrenia patients (11 males and one female, mean age 42 with a range from 35 to 46 years) were examined in comparison to 12 age- (mean age 42 with a range from 36 to 52 years) and sex-matched normal control subjects. Age was matched for the group and not on one-to-one bases. All patients were on typical neuroleptics (mean chlorpromazine equivalent dosage of 280 mg). Subjects with a documented diagnosis of alcohol or drug dependence were excluded. Schizophrenia patients had a negative urine drug screen (UDS) at the time of recording and had no drug or alcohol use for the month preceding the recording. This was verified with the primary treating clinician. Normal control subjects were instructed not to drink any alcohol for the 24 h preceding recording. While 10 of the 12 patients were smokers, only four of the control subjects smoked. All smokers were allowed to smoke up to 45 min prior to recording. This time inside the smoke-free lab environment was needed to prepare the subject for recording. Schizophrenia patients were administered the PANSS (Kay et al., 1987) and the SCID for DSM-IIIR by a fully trained clinical research assistant (master's level) under the supervision of one of the co-investigators. Normal control subjects were administered the screening version of the SCID. Normal subjects had no immediate family relatives with a history of psychiatric disorders.

2.2. Sensory gating evoked potential paradigms

2.2.1. Identical paired-clicks:

The inhibitory capacity of the brain was measured using identical pairs of clicks. In paired-click paradigms, two identical stimuli are presented binaurally with a 500-ms Inter-Stimulus Interval (ISI). This ISI has been shown to provide maximum differentiation between the gating capacities of normal and schizophrenia patients

(Nagamoto et al., 1989). The pairs are repeated every 8 s allowing for recovery of the neuronal pools generating the responses (Zouridakis and Boutros, 1992). Stimulus presentation continues until 60 artifact-free trials are collected. Responses to the first stimulus (S1) and the second stimulus (S2) are averaged separately. The auditory sensory inhibitory (i.e. gating) capacity is measured by dividing the amplitude of S2 responses by the amplitude of the S1 responses (S2/S1 ratio) and multiplying this ratio by 100. Lower S2/S1 ratios are assumed to reflect more sensory inhibition or more intact 'gating-out'.

2.2.2. Non-identical-pair paradigm

Non-identical-pair paradigms are similar to the identical pair paradigm except that the two clicks in each pair (S1 and S2) are different. In this paradigm the frequency of the second stimulus (S2) is higher (1500 Hz) than that of the first stimulus (S1) (1000 Hz). The S1 stimulus is consistent between the two conditions so direct comparison between the two conditions can be made. This paradigm is the principal measure of dishabituation in this project.

2.2.3. Short-trains paradigm

In this paradigm, trains of five identical stimuli are predictably followed by a sixth deviant stimulus. An ISI of 500 ms separates the stimuli in each train and an 8-s interval separates the trains. The degree of habituation of the identical stimuli can be used to assess the inhibitory capacity of the brain. Operationally, the S5/S1 ratio reflects the degree of habituation (inhibitory capacity) with four repetitions. Sensory dishabituation (gating-in) is measured by dividing the amplitudes of the responses resulting from the deviant stimulus by those resulting from the first or the fifth stimulus of the train. The same frequencies utilized in the non-identical-pair paradigm were used.

All stimuli were clicks of 4-ms duration with 1-ms rise and fall times. The pairs were repeated every 8 s. Data acquisition stopped automatically when 60 EP sweeps were collected. Clicks were 90 dbSPL as measured at the ear using a measure-and-hold digital sound meter (Tandy Corp). All clicks were delivered binaurally through calibrated earphones. Subjects were seated on a comfortable recliner with their heads fully supported.

2.3. Recording procedure

Each subject underwent all the conditions during two recording sessions in 2 consecutive days. All conditions were counterbalanced within and between subjects. All studies were performed between 10.00 and 12.00 h to avoid the confounding effects of possible diurnal variation. Subjects were escorted to the laboratory, a quiet and partially electrically shielded room. Monopolar recordings were made from silver/silver chloride disk electrodes applied at the Fz, Cz, Pz, and Oz locations and referred to linked ears. P50 measurements were made from the Cz electrode for consistency with the literature. The Oz electrode was used for monitoring levels of alertness (by monitoring alpha/theta activity). One channel was devoted to detecting eye movement artifacts recorded from a supraorbital electrode to the outer canthus. On line EEG artifact rejection allowed for trial rejection when activity in any channel exceeded 75 μV (Neuroscan Software, Herndon, VA). Electrical signals were amplified 20 000 times by Grass amplifiers with band-pass filters set at 0.05 and 300 Hz, and digitized at 1000 Hz for on-line averaging. The main frequency of the P50 component is 40 Hz (Clementz et al., 1997). In order to decrease the noise to signal ratio we further refiltered the EEG data between 10 and 50 Hz (Jerger et al., 1992).

EEG recording started 50 ms prior to stimulation and extended to 200 ms. Subjects were first given a trial run (without recording) to increase their familiarity with the protocol and to decrease their level of anxiety. During this run, the ongoing EEG was monitored to decide whether excessive muscular artifact was present. The technician worked with the subjects to get them to relax enough to decrease such activity as much as possible. Subjects were asked to stay alert. They were not required to perform any task and were not informed about the details of the nature of the paradigms. Once the actual recording started, the ongoing EEG was continuously monitored on an oscilloscope to assure alertness. If theta activ-

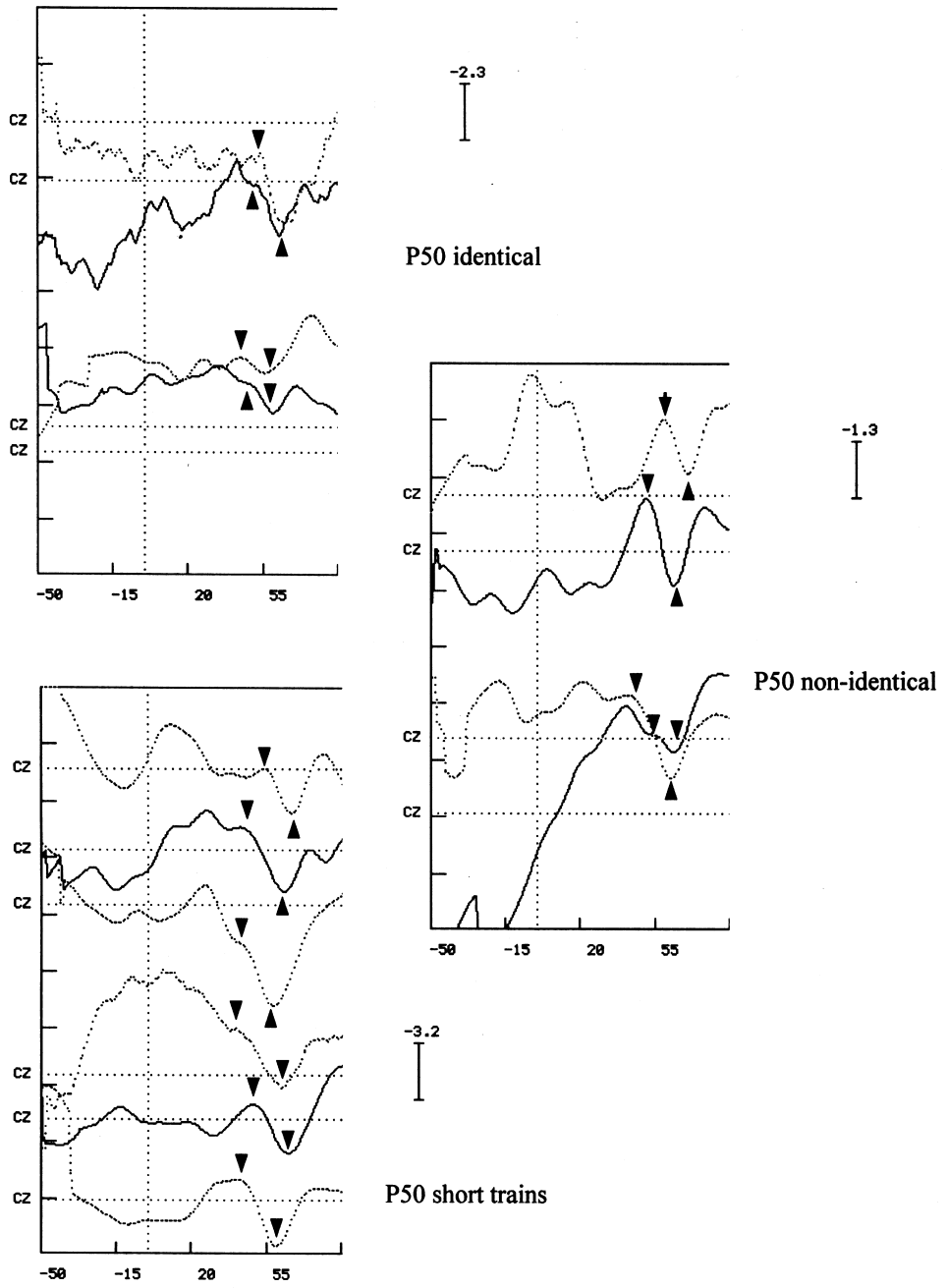

Fig. 1. Group averages of the P50 EP (individual peaks superimposed), in normal (bottom tracings) and schizophrenia (top tracings) subjects, utilizing identical pairs (top left graph), non-identical pairs (middle right graph), and short trains (lower left graph). The lower grand average of each pair of tracings represents S1 and the top represents S2. For short trains the lower tracing represents S1, the middle tracing represents S5, and the upper tracing represents S6.

ity appeared, the technician interacted with the subject to restore alpha or beta activity. If theta activity persisted for more than 10 s, the study was interrupted and subjects were allowed to stretch. Interruption was limited to 30 s.

A wave identified as the P50 component had to meet the following criteria: (1) the wave is the second major positive component between 30 and 80 ms post-stimulation and is preceded by the Pa wave in the 15–40-ms range. The Pa component usually occurs between 15 and 40 ms from stimulus onset (Erwin and Buchwald, 1986). In the rare situation that a Pa component is not identifiable, the largest positive deflection between 40 and 80 ms will be taken as the P50; and (2) it must be seen in at least one additional channel besides Cz.

2.4. Statistical analysis

Repeated measures analysis of variance (ANOVA; GLM Procedure) was performed for comparable data from all conditions of the same paradigm with 'group' as the independent variable and 'sensory gating ratio measures' as the dependent variables. Sensory gating, derived from averaged P50 or N100 EPs, was calculated by dividing the amplitude of the response to the S2 stimulus by the amplitude of the response to the S1 stimulus and multiplying this ratio by 100. If the amplitude of the S2 response was larger than the amplitude of the S1 response, the ratio was maximized at 200%. This is necessary to prevent skewing the data by a single (or few) large ratios. If the S2 response could not be found within 10 ms (for the P50) or 20 ms (for N100) of the latency of S1 response in the same trial, the response was assumed to have been completely attenuated. A 0.01-μV amplitude was entered to allow calculating this data point.

3. Results

3.1. Preattentive (P50) sensory gating measures

With group (normal vs. schizophrenia) as the independent variable, and S2/S1 ratios (derived from two paired-click paradigms) and S6/S5 ratios (derived from the short-train paradigm) as the dependent variables, there was an overall effect of paradigm (ratio) by group interaction ($F = 4.131$, d.f. = 2,28, $P < 0.03$).

3.1.1. Sensory-gating out

In the identical-pair paradigm, the two groups differed significantly, with schizophrenia patients exhibiting much less attenuation of the amplitude of the S2 P50 response and higher S2/S1 ratios as compared to normal control subjects ($51 \pm 44\%$ for normal subjects and $142 \pm 58\%$ for schizophrenia subjects) ($F = 7.519$, d.f. = 1,21, $P < 0.02$; Fig. 1, upper left panel). The degree of attenuation of the P50 responses to the fifth repeating stimulus (S5), of the short-train paradigm, was determined by dividing the S5 amplitude by the S1 amplitude. The S5/S1 ratio was, therefore, a measure of gating-out. A mean P50 S5/S1 ratio of $69 \pm 62\%$ was found for the normal subjects and $109 \pm 84\%$ for schizophrenia subjects ($F = 1.274$, d.f. = 1,19, $P = 0.275$).

3.1.2. Sensory-gating in

In the non-identical-pair paradigm, normal control subjects tended to augment the S2 P50 amplitudes (S2/S1 $100 \pm 67\%$) while schizophrenia patients tended to inhibit the S2 P50 responses (S2/S1 $76 \pm 67\%$), but the difference did not reach statistical significance due to significant overlap ($F = 0.457$, d.f. = 1,21, P = NS; Fig. 1 right panel). Table 1 shows the mean and S.D. values of the amplitudes of the P50 and N100 S1 and S2 responses and S2/S1 ratios in the two groups.

Utilizing the short-train paradigm, significant differences were found between the two groups (Table 2). The P50 amplitude tended to respond differently in the two groups. This difference occurred in a direction similar to that noted with the paired-click conditions. The S6/S2 ratios for the two groups were calculated. Normal subjects increased the amplitudes of their P50 EP components in response to the deviant stimulus (S6) resulting in higher S6/S2 ratios. The P50 S6/S2 ratios of normal control subjects were $150 \pm 90\%$ while schizophrenia patients had S6/S2 ratios of 50 ± 50 ($F = 6.930$, d.f. = 1,16, $P < 0.02$). Simi-

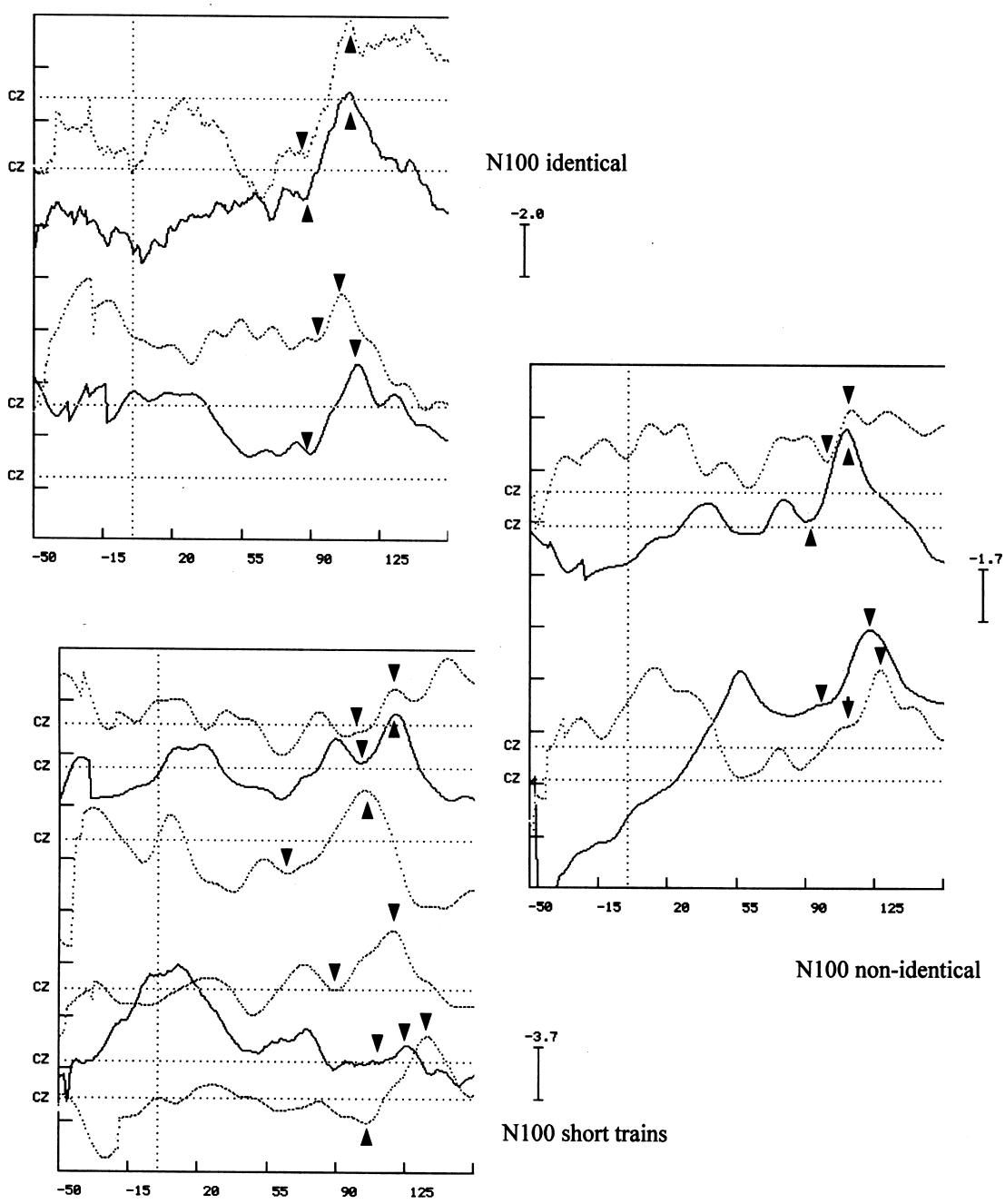

Fig. 2. Group averages of the N100 EP (individual peaks superimposed), in normal (bottom tracings) and schizophrenia (top tracings) subjects, utilizing identical pairs (top left graph), non-identical pairs (middle right graph), and short trains (lower left graph). The lower grand average of each pair of tracings represents S1 and the top represents S2. For short trains, the lower tracing represents S1, the middle tracing represents S5, and the upper tracing represents S6.

Table 1
Mean and S.D. values of the amplitudes of the P50 and N100 responses to S1, S2 and the S2/S1 ratios of the two groups

	Normal subjects			Schizophrenia subjects		
	S1 (μV)	S2 (μV)	S2/S1 (%)	S1 (μV)	S2 (μV)	S2/S1 (%)
Identical P50	3.3 ± 2.1	1.0 ± 0.08	51 ± 44[a]	2.5 ± 1.8	3.3 ± 1.9	142 ± 58
Non-identical P50	2.3 ± 1.9	2.3 ± 2.9	100 ± 67[a]	3.0 ± 2.6	1.8 ± 1.7	76 ± 67
Identical N100	4.7 ± 3.6	1.7 ± 1.7	33 ± 17[b]	4.4 ± 2.3	5.3 ± 5.2	130 ± 93[c]
Non-identical N100	3.4 ± 2.5	4.1 ± 3.2	144 ± 87[b]	4.8 ± 2.9	2.9 ± 2.5	60 ± 32[c]

[a] $P < 0.02$.
[b] $P < 0.001$.
[c] $P < 0.008$.

larly, schizophrenia patients tended to exhibit lower S6/S5 ratios ($F = 3.805$, d.f. = 1,19, $P < 0.07$).

3.2. Early-attentive (N100) sensory gating measures

Data derived from the N100 component (early-attentive gating) show a strong paradigm (ratio) by group interaction ($F = 9.121$, d.f. = 2,28, $P < 0.003$).

3.2.1. Sensory-gating out

In the identical-pair paradigm, schizophrenia patients exhibited much less attenuation of S2 N100 EPs and higher S2/S1 ratios as compared to normal control subjects (33 ± 17% for normals and 130 ± 93% for schizophrenia patients) ($F = 13.882$, d.f. = 1,21, $P < 0.001$; Fig. 2, upper left panel). The degree of attenuation of the N100 responses to the fifth (S5) repeating stimulus was determined by dividing the S5 amplitude by the S1 amplitude. A mean N100 S5/S1 ratio (short-train) of 70 ± 28% was found for the normal subjects and 101 ± 69% for the schizophrenia subjects ($F = 3.553$, d.f. = 1,19, $P < 0.08$).

When two measures of gating-out were compared to each other (i.e. S2/S1 from the identical-pair paradigm and S5/S1 from the short-train paradigm), no significant differences were found for the N100 ($F = 2.401$, d.f. = 1,19, $P = 0.141$) or the P50 ($F = 1.005$, d.f. = 1,19, $P = 0.331$).

3.2.2. Sensory-gating in

In the non-identical-pair paradigm, a significant difference in the degree of attenuation of the N100 responses to S2 stimuli was found, with schizophrenia patients inhibiting (instead of enhancing) their responses to the deviant stimuli as compared to normal control subjects (144 ± 87% for normals and 60 ± 32% for schizophrenia

Table 2
Mean and S.D. values of the P50 and N100 amplitudes to S1, S2, S5, and S6 stimuli and the S2/S1, S6/S1, S6/S2, and S6/S5 ratios of the two groups

		S1 (μV)	S2 (μV)	S5 (μV)	S6 (μV)	S2/S1 (%)	S6/S1 (%)	S6/S2 (%)	S6/S5 (%)
Cont.	P50	3.7 ± 3.3	2.6 ± 2.2	2.6 ± 2.9	4.0 ± 3.8	0.9 ± 0.7	1 ± 0.6	1.5 ± 0.9[a]	1.3 ± .6
Schiz.	P50	2.9 ± 1.8	3.7 ± 3.7	3.9 ± 3.6	2.2 ± 2.6	1.4 ± 0.8	0.9 ± 0.9	0.5 ± 0.5[a]	0.7 ± .6
Cont.	N100	6.8 ± 5.5	4.8 ± 4.4	4.7 ± 4.5	7.4 ± 6.4	0.7 ± 0.5	1.1 ± 0.7	1.4 ± 0.7[c]	1.6 ± .7[b]
Schiz.	N100	6.1 ± 4.2	5.2 ± 3.8	6.0 ± 5.0	3.8 ± 3.6	0.9 ± 0.3	0.7 ± 0.5	0.8 ± 0.3[c]	0.7 ± .6[b]

[a] $P < 0.02$.
[b] $P < 0.01$.
[c] $P < 0.04$.

patients) ($F = 8.766$, d.f. = 1,20, $P < 0.008$; Fig. 2, right panel). When the short-trains paradigm was used to examine the N100 component, significant differences were also found between the two groups (Table 2). The N100 S6/S2 ratios differed between the groups with higher ratios among normal subjects ($140 \pm 70\%$) as compared to schizophrenia patients ($80 \pm 30\%$) ($F = 5.337$, d.f. = 1,16, $P < 0.04$). Similarly, schizophrenia patients had lower S6/S5 ratios ($70 \pm 60\%$) as compared to normal control subjects ($130 \pm 60\%$) ($F = 8.434$, d.f. = 1,19, $P < 0.009$; Fig. 2, lower left panel). The S6/S1 ratios did not differ between the groups ($F = 1.877$, d.f. = 1,19, $P = 0.188$ for the N100 and $F = 0.0$, $P = 0.9$ for the P50). Data derived from S3 and S4 were found previously not to contribute further to data derived from S1, S2, S5, and S6 (Boutros et al., 1997). In preliminary analysis, S3 and S4 data from the current sample also did not contribute further beyond data derived from the other stimuli in the short-train paradigm. We, therefore, omitted these data from the current presentation.

4. Discussion

The above data suggest that schizophrenia patients, as a group, have difficulties in the four aspects of sensory gating identified above. First, patients have difficulty inhibiting incoming irrelevant stimuli at a preattentive phase of information processing. This is evidenced by the well-documented decreased ability to attenuate the amplitude of the P50 response to repeating identical stimuli (Adler et al., 1982). Second, schizophrenia patients demonstrate a decreased ability to respond properly to incoming relevant input at the same pre-attentive phase of information processing. This is evidenced by a decreased ability to recover the P50 amplitude in response to stimulus change. Third, difficulty in inhibiting responses to incoming irrelevant stimuli can also be demonstrated at a later phase of information processing (N100) where attentional factors are known to play more of a role than with the earlier P50 component. Lastly, the data also suggest that the N100 component of schizophrenia patients is less likely to respond properly to stimulus change than is found for normal control subjects. The data further suggest that the N100 may be more sensitive to measures of sensory gating than is the P50. This finding suggests that the P50 and N100 gating indices may not be redundant measures of sensory gating mechanisms.

Physiological theories that have been proposed explain the decrease of amplitude with repetition of identical stimuli, vacillate between active inhibitory/excitatory mechanisms and passive habituation/dishabituation mechanisms. An 'active gating' theory suggests that the S1 stimulus creates local neuronal inhibitory activity that will specifically inhibit (and thus gate or filter out) the response to a second, identical stimulus. The second stimulus, being similar to the first one, carries no new information and, thus, is inhibited so as not to flood higher cortical centers. Another possible theory to explain the attenuating effect of a previously presented stimulus involves refractory periods ('passive gating' theory). If this explanation were true, the decreased amplitude of the S2 response would depend on the recovery status of the neuronal pool stimulated by the first stimulus. However, most neurons need only a few milliseconds to reset their ionic equilibrium and regenerate their internal energy (Volkov and Galazyuk, 1992). In anesthetized cats, it has been shown that maximum inhibition in the primary auditory cortex coincided with the development of inhibitory post-synaptic potentials (IPSP) in the cortical cells (Volkov and Galazyuk, 1992). The inhibitory effect of the stimulus was shown to last for several hundred milliseconds. In the early period of the inhibitory reaction (20–200 ms), 96% of neurons in the primary auditory cortex developed IPSPs. The subsequent period of inhibitory reaction (i.e. later than 200 ms) was characterized by a decrease in the efficiency of the inhibition. It is, thus, likely that the decreased sensitivity of neurons responding to auditory stimuli that are repeated every 500 ms is caused more by the development of an inhibitory process in the cortical neurons themselves rather than by blocking of the in-flow of afferent excitatory impulses (i.e. refractoriness). Freedman et al. (1991) postulated that the S1 stimulus excites both the

hippocampal pyramidal neurons, giving rise to the initial evoked response, and also activates inhibitory neurons that act as a comparator. Subsequent identical stimuli (S2 in identical pairs), arriving while the inhibitory (comparator) neurons are still active, produce diminished responses in the pyramidal neurons.

Two plausible explanations can be put forth to explain the dishabituating effects of deviant stimuli on the amplitude of the P50 and N100 EPs. A passive theory suggests that when a second (or subsequent) non-identical stimulus is presented, a different set, of not previously stimulated neurons, are stimulated resulting in an unhabituated response. Another plausible theory is that the presentation of a deviant stimulus will cause inhibition of the hippocampal inhibitory (comparator) neurons, activated by S1, and will allow the pyramidal neurons to respond to the deviant stimulus. Volkov and Galazyuk (1992) postulated that the synchronous activation of a great number of neurons of the cortex by a brief stimulus would result in the release of large quantities of inhibitory transmitter into the synaptic cleft. Such an activation would lead to a relatively prolonged hyperpolarization of post-synaptic neurons. With repetition of the stimulus, a constant release of small quantities of the transmitter into the synaptic cleft is postulated as an active mechanism to explain the continued inhibition. The continued release of the inhibitory transmitter is probably sensitive to the physical characteristics of the stimulus and will cease if the stimulus changes. This mechanism supports a more active inhibition with stimulus repetition (gating-out) and a less active mechanism for the cessation of the inhibition, when the stimulus changes after the initial presentation (gating-in). The current study did not attempt to address these complex neurophysiological issues. Future studies designed to examine the relative contribution of these different mechanisms to sensory gating will shed more light on the basic mechanisms underlying this complex function.

The cortex samples successive inputs in time chunks. Cortical mechanisms are primarily concerned with recording rapidly changing and successive inputs and processing information in narrow slices of time (Merzenich et al., 1993; Merzenich and Jenkins, 1995). Any substantially new input resets cortical dynamics and, with a variable delay ranging from 10 to several hundred milliseconds, re-initiates the sampling process. This reset delay is a function of both the immediately preceding input event (S1 in our paradigms) and the resetting event (S2 in non-identical pairs or S6 in the short trains).

The data presented above suggest that schizophrenia patients have a deficiency in both pre-attentive and early-attentive inhibitory capacity leading to decreased ability to inhibit or attenuate the amplitude of the evoked response with repetition of identical stimuli. The data also suggest that schizophrenia patients have deficient dishabituation mechanisms that are activated when the stimulus is changed (non-identical or short-train paradigms), leading to faulty attenuation of the response to novel or deviant stimuli. A schizophrenia subject will, thus, process faulty bits of information and use such faulty bits to build a whole faulty experience. These observations are direct evidence for faulty information processing in schizophrenia patients and are in agreement with theories of mal-processing of bits of information by these patients (Shakow, 1962; Callaway et al., 1965).

Some of the data presented above are difficult to explain in view of currently available theories of habituation and dishabituation. First, the S1 amplitudes of normal subjects were smaller in the non-identical pairs than in the identical pairs (not significantly) in response to the exact same stimuli. This difference may have contributed to the higher ratios in the non-identical condition. Similarly, S1 amplitudes for the short trains were higher than those for either the identical or non-identical pairs, for both the P50 and N100 EPs, again in response to the same stimuli. This is not entirely surprising in view of recent data suggesting significant differences between the degree of attenuation of EPs in trains vs. paired-click paradigms (Cardenas et al., 1997). Moreover, it is possible that the sixth (deviant) stimulus either primes the stimulated neuronal pool to the next train of stimuli or that the deviant stimulus more effectively terminates any lingering inhibitory ef-

fects of the preceding stimulus train. Finally, the higher amplitude responses to S5 (seen mainly in schizophrenia patients) suggest that some form of sensitization occurs in this group instead of the inhibition seen in normal subjects. Further speculation on the meaning of the data should await replication in a larger sample size study.

The number of subjects was too small to allow for correlational analyses between PANSS symptom clusters and the different sensory gating findings. Future studies with larger sample sizes should be able to ascertain whether such correlations exist. The fact that all patients were stable on antipsychotic medications adds to the difficulty in interpreting the data. Whether antipsychotic medications affect the different sensory gating components differently remains to be answered. In conclusion, based on the preliminary data presented in this article, we postulate that schizophrenia patients suffer from deficiencies in a number of components of sensory gating resulting from faulty hippocampal wiring and resulting in both a difficulty in habituating repetitious inputs and a difficulty in resetting their cortical dynamics in response to novel or deviant stimuli.

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