Sensory gating impairment associated with schizophrenia persists into REM sleep

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Abstract
Physiological measures of sensory gating are increasingly used to study biological factors associated with attentional dysfunction in psychiatric and neurologic patient populations. The present study was designed to assess sensory gating during rapid eye movement (REM) sleep in patients with schizophrenia, a population bearing a genetic load for gating impairment. Auditory event-related potentials (ERPs) were recorded in response to paired clicks during separate waking and overnight sleep recording sessions in controls and schizophrenia patients. Suppression of ERP component P50 was significantly impaired in the patient group during both waking and REM sleep, whereas the difference between groups for N100 gating was dependent on state. These results suggest that REM sleep is an appropriate state during which to assess P50 gating in order to disentangle the effects of state and trait on sensory gating impairment in other clinical populations.

Descriptors: Sensory gating, REM sleep, Schizophrenia, Auditory event-related potentials, P50, N100

Persons afflicted with schizophrenia suffer from, among other symptoms, dysfunction in the allocation of attention (McGhie & Chapman, 1961). For these individuals a perceptual impairment—an inability to ignore, or filter out, irrelevant sensory information—is paralleled by a neurophysiological abnormality in “sensory gating” (Cullum et al., 1993; Erwin, Turetsky, Moberg, Gur, & Gur, 1998). Typically, sensory gating is assessed by comparing the magnitude of evoked brain activity in response to repetitive auditory stimuli. After the first stimulus, electroencephalographic activity evoked by subsequent stimuli is attenuated (i.e., “gated”) in a majority of healthy persons. However, individuals with schizophrenia (Adler et al., 1982; Boutros, Zouridakis, & Overall, 1991; Erwin, Mawhinney-Hee, Gur, & Gur, 1991; Jerger, Biggins, & Fein, 1992; Judd, McAdams, Budnick, & Braff, 1992) and many of their unaffected first degree relatives (Clementz, Geyer, & Braff, 1997; Siegel, Waldo, Mizner, Adler, & Freedman, 1984; Waldo et al., 1994) do not exhibit this type of response inhibition, particularly for component P50 of the auditory event-related potential. Whether sensory gating measured physiologically correlates with behavioral measures of attentional filtering on a person-by-person basis remains controversial (compare Jin et al., 1998 to Light & Braff, 2000). Nevertheless, physiological gating abnormalities associated with schizophrenia have been linked to a specific chromosomal locus (15q14: Freedman et al., 1997). This same locus has subsequently been linked to a broader phenotype—diagnosis of schizophrenia (Riley et al., 2000; Stober et al., 2000)—consistent with the notion that sensory gating impairment, as measured electrophysiologically, is an inherited trait in families with a history of schizophrenia.

The relative ease of sensory gating assays, and an increasing understanding of the neural mechanisms responsible for this phenomenon (reviewed by Adler et al., 1998), make sensory gating an attractive variable for study in clinical research. For example, efforts are currently underway to relate sensory gating impairments to specific genetic polymorphisms in the promoter region of the human α7 nicotinic receptor gene (Leonard et al., 2001). Abnormalities in the expression and/or function of these low-affinity nicotine receptors are believed to underlie sensory gating deficits associated with schizophrenia (Leonard et al., 2000). Investigators are also beginning to employ sensory gating measures in attempts to understand the biological basis of other clinical syndromes associated with attentional dysfunction including attention-deficit/hyperactivity disorder (Olincy et al., 2000), post-traumatic stress disorder (Neylan et al., 1999; Skinner et al., 1999), drug dependence (Adler et al., 2001; Boutros et al., 2000; Patrick & Struve, 2000), and various neurological conditions (Ambrosini, DePasqua, Afra, Sandor, & Schoenen, 2001; Arciniegas et al., 2000; Jessen et al., 2001;
Teo et al., 1997). Because sensory gating measures are sensitive to state, particularly acute stress (Johnson & Adler, 1993; White & Yee, 1997), it is important in future studies to distinguish between transient gating impairments and gating abnormalities due to persistent brain modification caused by genetic program and/or environmental insult. This is especially true for reactive populations, such as children and traumatized individuals.

To overcome the potential confound of brain state, we propose to assess sensory gating during rapid eye movement (REM), or “paradoxical” sleep. REM sleep is characterized by a cessation of activity in the locus coeruleus (Hobson, McCarley, & Wyzinski, 1975), a brainstem nucleus providing the noradrenaline innervation for the entire brain. This is important because increased central noradrenergic activity is believed to underlie transient gating impairments associated with control subjects’ state (Adler, Pang, Gerhardt, & Rose, 1988; Adler et al., 1994; Stevens, Meltzer, & Rose, 1993). It has recently been shown that sensory gating can be assessed during sleep in healthy adults, and that gating measures taken during REM sleep are within the previously established “normal” range for control subjects (Kisley, Olincy, & Freedman, 2001). However, it has not been shown that populations known to exhibit high rates of gating impairment during waking—such as persons with schizophrenia—also exhibit high rates of gating impairment during REM sleep. Such a demonstration would establish that (a) sensory gating abnormalities associated with schizophrenia are not state dependent, and (b) REM sleep is an appropriate brain state under which to measure sensory gating in future clinical studies.

The present study was designed to test three novel hypotheses: (a) patients with schizophrenia differ from control subjects in their ability to filter auditory stimuli, as measured by a paired-click paradigm, during REM sleep; (b) this difference between groups is similar across waking and REM sleep states, consistent with a state-independent impairment; (c) sensory gating varies over the course of a REM sleep period for schizophrenia patients. The third hypothesis was tested because previous studies have shown that P50 gating can be transiently normalized in schizophrenia patients immediately after awakening from a bout of non-REM sleep (Griffith & Freedman, 1993; Griffith, Waldo, Adler, & Freedman, 1993). Therefore, because REM sleep follows non-REM sleep in adults, we expected schizophrenia patients to exhibit “normal” P50 gating during the first few minutes of a REM sleep period. In addition to, and for comparison with, event-related potential component P50 (i.e., P1 or P2), we assessed the state-dependence of wave N100 (i.e., N1 or N2), as this wave is also commonly employed to study sensory gating.

Methods

Participants

Procedures were approved by the Colorado Multiple Institute Review Board. Participants gave written informed consent, and received monetary compensation upon completion of the study. Exclusion criteria for all participants were current illicit substance use and past traumatic brain injury (requiring loss of consciousness lasting at least 5 min after head injury), both of which have been shown to affect sensory gating measures (e.g., Arciniega et al., 2000; Boutros et al., 2000). Also, patients taking clozapine were excluded because this atypical antipsychotic has been shown to modify sensory gating measures (Nagamoto et al., 1999). Diagnosis of schizophrenia was confirmed for all patients by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I: First, Gibbon, Spitzer, & Williams, 1996) except for one man, who did not complete a diagnostic interview, but met diagnostic criteria based on informal interview and review of medical records. Eleven patients with schizophrenia completed the study; 1 was excluded from analysis as he exhibited less than 5 min of REM sleep, leaving 5 men and 5 women (mean age 41.6, range 20–50 years). The control group, consisting of volunteers from the local community, also consisted of 5 men and 5 women, and mean age of 34.4 years (range 21–47) was not significantly different from the patients. Three patients and 1 control were smokers. All patients were taking antipsychotic medications (2 olanzapine, 2 quetiapine, 2 risperidone, 1 olanzapine and risperidone, 1 quetiapine and thiothixene, and 2 loxapine). One patient on loxapine was taking an anticholinergic medication.

Electrophysiology

Ongoing electroencephalographic (EEG) and stimulus-evoked brain activity were recorded (Neuroscan Acquisition System: SynAmps amplifiers, Scan 4.1 acquisition software; Sterling, VA) from each participant during two separate sessions: one during daytime waking, and one during overnight sleep. Two patients and 3 controls preferred to undergo the overnight sleep recording before the daytime waking recording. Sleep staging and event-related potentials measurements were taken from vertex (Cz) referenced to right ear. Electrooculogram (EOG) was recorded in a bipolar configuration between electrodes directly superior and lateral to the left eye. During overnight recordings, the electromyogram (EMG) was also recorded with a bipolar submental configuration (Rechtschaffen & Kales, 1968). A ground electrode was attached to the left ear. All electrodes were gold-plated 10-mm disc (Grass; West Warwick, RI), affixed with Ten20 conductive paste (D.O. Weaver and Co.; Aurora, CO) and surgical tape (no tape was used for ear-clip electrodes). All impedances were maintained below 10 kΩ.

Average auditory event-related potentials were computed from the EEG activity immediately following acoustic clicks (1 ms duration), which were delivered to the participants through insert earphones. The click intensity was 40 dB above hearing level. Before recording, both ears were tested independently for all participants (method of limits) to ensure normal hearing. Clicks occurred in pairs (0.5-s interclick interval) and pairs occurred every 10 s.

During the waking recording, supine participants were instructed to keep their eyes open and still during the click pairs. After 5 min acclimatization, recording began and lasted until 20 min of data had been acquired. Typically participants took one break during the recording. For 2 control participants, recording was paused because of the presence of slow waves and vertex sharp waves in the EEG, and the participants were roused. Overnight sleep recordings were performed in the same laboratory using identical equipment. The acoustic clicks occurred continuously throughout the night.

For acquisition, EEG signals were amplified 5,000 times and filtered between 0.1 and 200 Hz, EOG amplified 1,000 times and filtered between 0.1 and 100 Hz, EMG amplified 12,500 times and filtered between 5.0 and 200 Hz. All channels were sampled at 1000 Hz. Continuously recorded data were converted from Neuroscan’s Scan 4.1 software format to ASCII format, then
imported into the Matlab software package (Mathworks; Natick, MA) for further analysis with custom programs.

**Isolation of REM Sleep Episodes for Event-Related Potential Measurement**
Continuous overnight recordings were divided into 20-s epochs for scoring of sleep stages, and initially screened for REM sleep periods by analyzing EEG power in the spindle (12–14 Hz) band, total EOG power, and total EMG power. Putative REM episodes were then identified as periods of greatly reduced spindle power, increased EOG power, and reduced submental EMG power (for more detail and an example, see Kisley et al., 2001). Final determination of sleep stage was achieved by visual inspection of the EEG, EOG, and EMG signals in 20-s epochs, and the application of traditional criteria as described in Rechtschaffen and Kales (1968) by a blind rater. Stage I sleep was discriminated from REM sleep by the absence of rapid eye movements and elevated EMG activity. Stage II was identified by the presence of spindle activity and K-complexes in the EEG. Stages III and IV were characterized by the presence of delta waves (up to 2 Hz) in the EEG.

Average auditory event-related potentials were computed from EEG signals recorded during the initial 20 min of the first REM episode of the night that lasted 20 min or longer. The duration was set at 20 min because all participants exhibited REM periods at least this long. A distinct “REM episode” was considered to begin when two consecutive 20-s epochs were scored as REM sleep, and end when three or more consecutive epochs were scored as non-REM sleep or waking. Defined in this manner, a REM episode could include epochs containing movement artifact, arousals, K-complexes, and spindles as long as the participant returned to REM sleep within two epochs.

**Sensory Gating Paradigm and the T/C Ratio**
Pairs of clicks (0.5-s interclick interval) were presented every 10 s throughout the recording session, and average event-related potentials computed separately for each click of the pair. The amplitude of wave P50 to the second (test) click of a pair was then compared with P50 magnitude evoked by the first (conditioning) click. Specifically, a ratio of the magnitudes, the test/conditioning or T/C ratio, was computed to quantify sensory gating. A T/C ratio close to 0 indicates robust suppression (very small test response compared with conditioning response) and a T/C ratio of 1 indicates essentially no sensory gating (test and conditioning responses were comparable in magnitude). In the general population, T/C ratios for component P50 range from 0 to well over 1, but are generally below 0.4 for subjects without a personal or family history of psychosis (Siegel et al., 1984; Waldo et al., 1994). Individuals with schizophrenia usually have T/C ratios above 0.5 (e.g., Adler et al., 1982). For the present study, to prevent bias from outliers, T/C ratios above 2.0 were assigned a value of 2.0. This affected the P50 T/C ratio for 2 patients during the waking recording and 2 patients during the REM sleep recording.

**Computation of Average Event-Related Potentials and Component Definition**
For both states of vigilance, average event-related potentials were computed from single-trial responses evoked during carefully defined 20-min intervals. During waking, the average was computed from the first 20 contiguous minutes of recording time following the initial 5-min acclimatization. The 20-min periods utilized for REM sleep are detailed above in the description of sleep stage scoring. Single-trial event-related potentials, epoched from 100 ms before to 200 ms after each click, were detrended (linear) and subject to artifact rejection. In particular, if the signal on any channel (EEG, EOG, EMG) exceeded ± 75 μV during an event-related potential epoch, that trial was excluded from further analysis. After this step, the number of single trials remaining for averaging ranged from 72 to 116 for controls and 77 to 111 for patients during the waking recording, and from 97 to 113 for controls and 99 to 113 for patients during the analyzed REM episode. Average waveforms computed from the remaining single trials were band-pass filtered between 5 and 100 Hz to accentuate component P50 (Suzuki, Kobayashi, & Hirabayashi, 1983). This filter was applied both forward and reverse to eliminate phase distortion (Matlab’s “filtfilt” function).

Component P50 in response to the conditioning click was defined as the first positive waveform peak between 50 and 75 ms. When no such peak was evident (N = 1 control subject), the most positive peak between 40 and 50 ms was used. Component P50 for the test click was determined the same way, with the restriction that the peak latency must be within ± 10 ms of the conditioning latency. If no peak satisfied these criteria, the P50 test amplitude was taken as zero. To maintain consistency with previous sensory gating literature, P50 magnitude was measured from the preceding negative trough, the N40 (Nagamoto, Adler, Waldo, & Freedman, 1989). When an expected peak or trough was absent, the value at the nearest “shoulder” (i.e., point of minimal slope) was used. All subjects exhibited conditioning P50 waves larger than 0.5 μV during the waking state.

To make selection of component N100 easier, average waveforms were filtered again with a low-pass at 50 Hz to remove small and fast fluctuations. N100 was then defined for the conditioning click as the first negative trough later than 75 ms. The test N100 was similarly identified, with the added restriction that the trough must be within ±20 ms of the conditioning latency. N100 amplitude was measured from the preceding positive peak, which was usually the P50, but occasionally a distinct positive component occurring after P50 (Kisley et al., 2001). Although N100 amplitude is often measured relative to prestimulus baseline activity, we employed a peak-to-trough measurement to maintain consistency with the method of analysis for component P50. To ensure that this approach did not bias the present results, we repeated all analyses of N100 variables based on amplitude measures from baseline (mean over 50 ms preceding clicks). Although the mean N100 amplitudes were smaller with this method, the results of statistical comparison between groups and across states were essentially unchanged (not shown).

**Statistics**
Event-related potential and sensory gating measures were compared across groups by one-way ANOVA, computed separately for the waking and REM-sleep states. The effect of state on sensory gating, particularly the expected difference between groups, was assessed by repeated measure ANOVA: waking versus REM as within-group factors and control versus patient as between-group factors. To investigate whether event-related potential and sensory gating measures changed over time during a REM episode, repeated measures ANOVA was also applied to serial measurements taken at 5-min intervals. To protect against Type I errors, the degrees of freedom for all
repeated measures ANOVAs were adjusted by the method of Greenhouse and Geisser (1959).

Results

Comparison of Groups during the Waking State
Sensory gating measures taken during the waking state differed between control and schizophrenia groups. In general, control subjects exhibited strong suppression of event-related potential components P50, mean T/C = 0.39, range 0.01–1.22, and N100, mean 0.24, range 0.00–0.68, whereas schizophrenia patients did not, P50: mean 0.93, range 0.04–2.00; N100: mean 0.85, range 0.24–1.83. Figures 1 and 2 exemplify event-related potentials recorded from a control and patient, respectively. T/C ratios were significantly different between groups for both P50, F(1,18) = 5.20, p = .035, and N100, F(1,18) = 12.24, p = .003. No other event-related potential variables were significantly different for wave P50, but N100 test amplitude was significantly larger in patients, F(1,18) = 7.91, p = .012. Results are summarized in Tables 1 and 2.

Comparison of Groups during the REM-Sleep State
Sensory gating measures taken during REM sleep also differed between control and schizophrenia groups. Control subjects, in general, exhibited strong suppression of event-related potential components P50, mean T/C = 0.20, range 0.00–0.57, but not N100, mean T/C = 0.89, range 0.36–1.93; schizophrenia patients did not suppress either component during REM sleep, P50: mean T/C = 0.93, range 0.00–2.00; N100: mean 0.74, range 0.17–1.81. Event-related potentials recorded from 2 schizophrenia patients during REM sleep are shown in Figure 3. T/C ratios were significantly different between groups for component P50, F(1,18) = 9.25, p = .007, but not N100. Unlike waking, P50 test amplitude differed between groups, F(1,18) = 6.75, p = .018. Results are summarized in Tables 3 and 4.

REM sleep variables were assessed to ensure that the observed difference in P50 sensory gating between groups was not simply due to differences in sleep architecture. Although there was a trend suggesting that controls had more distinct REM episodes during the entire night than patients, mean = 3.0 versus 1.9, p = .051, there was no significant difference between groups in the total number of minutes constituting “REM episodes” or in the total percentage of epochs during those episodes considered to be classical “REM epochs” (Table 5). Considering only those REM episodes used for computing average event-related potentials, there was no significant difference between groups in the rank of REM episode used (i.e., first of the night, second, etc.), the overall length of those episodes, or the percentage of epochs within those episodes that were scored as REM sleep (Table 6).
Effect of State on Sensory Gating Measures

To assess the effect of state on sensory gating, repeated measures ANOVAs were applied across state (waking vs. REM sleep), with diagnosis (control vs. schizophrenia) as a between-groups factor. For component P50, no significant state or State × Diagnosis effects were found for T/C ratio, conditioning, or test amplitudes or latencies. For component N100, significant effects of state on T/C ratio, $F(1,18) = 5.19$, $p = .035$, and conditioning amplitude, $F(1,18) = 15.78$, $p = .001$, were found. Significant State × Diagnosis effects were also found for N100 T/C ratio, $F(1,18) = 10.03$, $p = .005$, and test amplitude, $F(1,18) = 18.42$, $p < .001$. This was expected, as N100 sensory gating differed between groups during waking, but not during REM sleep (see above). A graphical representation of the effect of state on P50 and N100 sensory gating differences between control and schizophrenia groups is shown in Figure 4.

Table 1. P50 Variables Compared between Controls and Patients during Waking

<table>
<thead>
<tr>
<th></th>
<th>Controls: Mean (SD)</th>
<th>Patients: Mean (SD)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditioning amplitude ($\mu$V)</td>
<td>1.51 (0.62)</td>
<td>1.63 (1.27)</td>
<td>.789</td>
</tr>
<tr>
<td>Test amplitude ($\mu$V)</td>
<td>0.67 (0.81)</td>
<td>1.85 (2.58)</td>
<td>.183</td>
</tr>
<tr>
<td>Conditioning latency (ms)</td>
<td>56.8 (7.9)</td>
<td>55.6 (3.4)</td>
<td>.665</td>
</tr>
<tr>
<td>Test latency (ms)</td>
<td>58.5 (8.0)</td>
<td>56.6 (4.7)</td>
<td>.524</td>
</tr>
<tr>
<td>T/C ratio</td>
<td>0.39 (0.35)</td>
<td>0.93 (0.66)</td>
<td>.035</td>
</tr>
</tbody>
</table>

Notes: One-way ANOVA 1,18 df. Bold entries highlight significant differences between groups.

Table 2. N100 Variables Compared between Controls and Patients during Waking

<table>
<thead>
<tr>
<th></th>
<th>Controls: Mean (SD)</th>
<th>Patients: Mean (SD)</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditioning amplitude ($\mu$V)</td>
<td>5.66 (2.02)</td>
<td>4.37 (1.62)</td>
<td>.133</td>
</tr>
<tr>
<td>Test amplitude ($\mu$V)</td>
<td>1.05 (1.03)</td>
<td>3.74 (2.84)</td>
<td>.012</td>
</tr>
<tr>
<td>Conditioning latency (ms)</td>
<td>96.1 (9.8)</td>
<td>92.2 (8.1)</td>
<td>.344</td>
</tr>
<tr>
<td>Test latency (ms)</td>
<td>92.8 (14.3)</td>
<td>87.3 (9.8)</td>
<td>.340</td>
</tr>
<tr>
<td>T/C ratio</td>
<td>0.24 (0.26)</td>
<td>0.85 (0.49)</td>
<td>.003</td>
</tr>
</tbody>
</table>

Notes: One-way ANOVA 1,18 df; test latency 1,17 df. Bold entries highlight significant differences between groups.
34

Table 3. P50 Variables Compared between Controls and Patients during REM Sleep

<table>
<thead>
<tr>
<th></th>
<th>Controls: Mean (SD)</th>
<th>Patients: Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditioning amplitude (µV)</td>
<td>0.79 (0.29)</td>
<td>1.40 (1.02)</td>
<td>.085</td>
</tr>
<tr>
<td>Test amplitude (µV)</td>
<td>0.18 (0.18)</td>
<td>1.31 (1.36)</td>
<td>.018</td>
</tr>
<tr>
<td>Conditioning latency (ms)</td>
<td>57.2 (2.4)</td>
<td>58.3 (5.7)</td>
<td>.579</td>
</tr>
<tr>
<td>Test latency (ms)</td>
<td>56.4 (4.9)</td>
<td>57.4 (9.6)</td>
<td>.780</td>
</tr>
<tr>
<td>T/C ratio</td>
<td>0.20 (0.22)</td>
<td>0.93 (0.73)</td>
<td>.007</td>
</tr>
</tbody>
</table>

Notes: One-way ANOVA 1,18 df; test latency 1,15 df. Bold entries highlight significant differences between groups.

Table 4. N100 Variables Compared between Controls and Patients during REM Sleep

<table>
<thead>
<tr>
<th></th>
<th>Controls: Mean (SD)</th>
<th>Patients: Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditioning amplitude (µV)</td>
<td>3.72 (0.86)</td>
<td>2.76 (1.13)</td>
<td>.046</td>
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<tr>
<td>Test amplitude (µV)</td>
<td>3.23 (1.85)</td>
<td>2.05 (1.52)</td>
<td>.138</td>
</tr>
<tr>
<td>Conditioning latency (ms)</td>
<td>98.1 (4.8)</td>
<td>99.0 (17.2)</td>
<td>.875</td>
</tr>
<tr>
<td>Test latency (ms)</td>
<td>94.0 (12.4)</td>
<td>104.3 (20.6)</td>
<td>.193</td>
</tr>
<tr>
<td>T/C ratio</td>
<td>0.89 (0.48)</td>
<td>0.74 (0.51)</td>
<td>.507</td>
</tr>
</tbody>
</table>

Notes: One-way ANOVA 1,18 df. Bold entries highlight significant differences between groups.

Table 5. REM Sleep Variables for Entire Night

<table>
<thead>
<tr>
<th></th>
<th>Controls: Mean (SD)</th>
<th>Patients: Mean (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of REM periods ≥5 min</td>
<td>3.00 (1.33)</td>
<td>1.90 (0.99)</td>
<td>.051</td>
</tr>
<tr>
<td>Total amount of REM sleep (min)</td>
<td>26.2 (17.3)</td>
<td>51.1 (26.2)</td>
<td>.173</td>
</tr>
<tr>
<td>% of epochs within REM periods scored as “REM”</td>
<td>92.7 (4.9)</td>
<td>95.5 (4.3)</td>
<td>.185</td>
</tr>
</tbody>
</table>

Note: One-way ANOVA 1,18 df.

Discussion

Sensory gating measures differed significantly between control and schizophrenia groups during waking and during REM sleep. In particular, patients with schizophrenia exhibited impaired gating of auditory event-related potential component P50 across both states. In contrast, the difference between groups in gating of component N100 was only found during the waking state. For this wave, control subjects exhibited a relative lack of response suppression during REM sleep, and corresponding T/C ratios comparable to that of the schizophrenia group. However, given the relatively small sample size used in this study, only a relatively large difference in N100 gating between groups would be detectable.

The central goal of this research was to demonstrate that impairments in P50 sensory gating associated with schizophrenia are present not only during the waking state, but also during REM sleep. Such a demonstration is useful because it (a) confirms the state independence of the P50 gating deficit in schizophrenia, and (b) validates the use of REM sleep-based gating paradigms for future studies designed to discriminate between sensory gating deficits due to state-related effects such as stress and lasting brain lesions caused by developmental program, personal experience, or some combination thereof. Stronger justification for measuring sensory gating during REM sleep could be generated in future studies by demonstrating that the stability of sensory gating, across multiple recording sessions, is higher in this state than during waking.
It should be noted that the manifestation of acute stress may not be totally neutralized during REM sleep. Studies of so-called oniric behavior and functional brain activation support the notion that paradoxical sleep is often associated with neural activity linked to the emotional experience (Jouvet, 1965; Henley & Morrison, 1974; Maquet et al., 1996). Further, it has been shown that both acute and chronic stress can affect the expression of REM sleep (e.g., Hefez, Metz, & Lavie, 1987; Rampin, Cespublio, Chastrette, & Jouvet, 1991). Nevertheless, once an organism enters REM sleep, the brainstem noradrenergic neurons—which are a central component of the CNS-mediated acute stress response (Johnson, Kamilaris, Chrousos, & Gold, 1992; Valentino, & Aston-Jones, 1995)—and autonomic arousal systems are quiescent, leading to a state described by Horne (2000) as “putative emotional inhibition.” Serotonin activity—which has also been shown to modulate sensory gating (Johnson, Stevens, & Rose, 1998)—is similarly dampened during REM sleep (Lydic, McCarley, & Hobson, 1983). At the least, then, REM sleep represents a state of reduced pharmacological confound compared to waking in the context of sensory gating assessment.

Another potential criticism of this study involves the observation that patients with schizophrenia often experience disrupted sleep patterns, including abnormal REM sleep architecture (Zarcone, 1988). However, whether these disturbances are inherent to the illness itself or due to chronic neuroleptic treatment remains controversial (Lauer, Schreiber, Pollmacher, Holsboer, & Krieg, 1997; Thaker, Wagman, & Tamminga, 1990). There is also indirect evidence that REM sleep itself is somehow qualitatively abnormal in schizophrenia (Roschke, Wagner, Mann, Prentice-Cuntz, & Frank, 1998). Regardless, we detected no differences in basic REM sleep variables between control and patient groups that could explain the observed difference in P50 sensory gating.

Finally, it should be noted that the present data do not necessarily confirm that the observed sensory gating impairment associated with schizophrenia is of identical neural origin in waking and REM-sleep states. It has been hypothesized that sensory gating deficits due to increases in P50 test amplitude might be fundamentally different than deficits caused by decreases in conditioning amplitude (e.g., Stevens, Kem, & Freedman, 1999). Although the T/C ratio significantly differed between control and patient groups during both states in the present study, P50 test amplitudes were significantly elevated in the patient group only during REM sleep (compare Tables 1 and 3). However, we suggest that this discrepancy between states is due to increased variability in test response amplitude during waking for both groups (note higher standard deviations during waking). In support of this, repeated measures analysis uncovered no significant changes in either conditioning or test P50 amplitudes from waking to REM sleep (see Results).
Comparison with Previous Studies

Sensory gating measures obtained during waking in the present study are consistent with previous reports from the past two decades (Adler et al., 1982; Boutros, Belger, Campbell, D’Souza, & Krystal, 1999; Erwin et al., 1991; Jerger et al., 1992; Judd et al., 1992). In particular, we found that response suppression of both auditory event-related potential components P50 and N100 was significantly impaired in patients with schizophrenia compared to healthy controls. Because abnormalities of P50 sensory gating associated with schizophrenia have been linked to a specific chromosomal locus (Freedman et al., 1997), we expected that this impairment would be expressed during REM sleep. In contrast, N100 gating was not significantly impaired in patients with schizophrenia compared to healthy controls. Because abnormalities of N100 gating associated with schizophrenia have been linked to a specific chromosomal locus (Freedman et al., 1997), we expected that this impairment would be expressed during REM sleep.

Patients taking clozapine were excluded from this study because Nagamoto et al. (1999) demonstrated that this medication, when taken over months, actually improves P50 sensory gating. Although evidence now exists that other atypical antipsychotic medications may improve sensory gating (Light, Geyer, Clementz, Cadenhead, & Braff, 2000; Yee, Nuechterlein, Morris, & White, 1998), patients taking these drugs (N = 8) were included in the present study due to difficulties in recruiting patients taking only traditional neuroleptics (N = 2). Although P50 gating in our schizophrenia group was significantly impaired compared to healthy controls, 3 of 10 patients did exhibit sensory gating measures within the normal range (T/C < 0.4: Siegel et al., 1984; Waldo et al., 1994) during REM sleep. Each of these 3 patients was taking a different atypical medication—olanzapine, quetiapine, and risperidone. A recent study suggests that all three of these medications can produce sensory gating improvements, but only in a relatively small number of schizophrenia patients (L. E. Adler, unpublished observations).

Previous studies have shown that sensory gating is transiently improved in schizophrenia patients when measurements are taken within a few minutes of awakening from a bout of non-REM sleep (Griffith et al., 1993; Griffith & Freedman, 1995). The mechanism for this phenomenon is believed to involve re-sensitization of low-affinity nicotine receptors during the progressively suppressed acetylcholinergic synaptic transmission that is associated with stages II, III, and IV sleep (Griffith et al., 1998). Because paradoxical sleep typically follows non-REM sleep, we expected to find that P50 gating was temporarily improved in schizophrenia patients during the first 5 min of REM sleep. This was observed in a subgroup of patients that exhibited only relatively deep non-REM sleep (i.e., stages II, III, and IV) immediately before the REM period, consistent with Griffith et al. (1993), who demonstrated that deeper non-REM sleep preceding a waking period leads to more detectable P50 gating improvement than does stage I and waking.
Conclusion
Previous research has shown that relatively complex differential processing of acoustic information continues during paradoxical sleep, as evidenced by the presence of event-related potential components P300 (Cote & Campbell 1999a, 1999b; Perrin, García-Larrea, Mauguier, & Bastuji, 1999; Sallinen, Kaartinen, & Lytinen, 1996) and mismatch negativity (Atienza, Cantero, & Gomez, 2000; Loewy, Campbell, & Bastien, 1996; Loewy, Campbell, de Lugt, Elton, & Kok, 2000; Nashida et al., 2000). The present study demonstrates that impairment of differential acoustic processing, as measured by P50 sensory gating, can also be expressed during this particular state. This finding validates potential future applications of REM-sleep-based sensory gating assays in clinical research, especially when variables associated with the waking state might confound measurement. Such applications are anticipated to include studies of sensory gating in infants and children at elevated risk for schizophrenia, family and genetic studies requiring very accurate phenotypic characterization, and studies of other clinical populations known to be reactive to stressful situations.

REFERENCES


