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Inhibition of the P50 Cerebral Evoked Response to Repeated Auditory Stimuli: Results from the Consortium on Genetics of Schizophrenia

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Abstract

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Conflict of Interest. Robert Freedman has a patent through the Department of Veterans Affairs on the sequence of CHR7. All other authors declare that they have no conflicts of interest.

Contributors. David L. Braff designed the Consortium on Genetics of Schizophrenia study. Ann Olincy and Robert Freedman analyzed the data and wrote the initial draft of the paper. Brandie Wagner performed the mixed model analysis of variance. Lawrence E. Adler and Gregory A. Light contributed to the protocol for evoked potential recording. All other authors participated in the design of the overall protocol, collection of the data, and discussions about its significance. All authors contributed to and have approved the final manuscript.

Inhibition of the P50 evoked electroencephalographic response to the second of paired auditory stimuli has been frequently examined as a neurophysiological deficit in schizophrenia. The National Institute of Mental Health Consortium on the Genetics of Schizophrenia (COGS) examined this endophenotype in a 7 center multi-site study. Recordings were analyzed from 181 probands with schizophrenia, 429 of their first degree relatives, and 333 community comparison control subjects. Most probands were being treated with second generation neuroleptic medications. Highly significant differences in P50 inhibition, measured as either the ratio of amplitudes or their difference in response to the two stimuli, were found between the probands and the community comparison sample. There were no differences between the COGS sites for these findings. For the ratio parameter, an admixture analysis indicated that nearly 40% of the relatives demonstrated deficiencies in P50 inhibition that are comparable to the deficit found in the probands. These results indicate that P50 auditory evoked potentials can be recorded across multiple sites and reliably demonstrate a physiological abnormality in schizophrenia. The appearance of the physiological abnormality in a substantial proportion of clinically unaffected first degree relatives is consistent with the hypothesis that deficits in cerebral inhibition may be a familial neurobiological risk factor for the illness.

Keywords

Schizophrenia; Evoked potentials auditory; Inhibition; Genetics

1. Introduction

Inhibition of the P50 component of the cerebral electroencephalographic evoked response to repeated auditory stimuli has been used to assess sensory gating dysfunction in schizophrenia (Erwin et al., 1991). Normal subjects show more inhibition of the response to the second of paired stimuli than persons with schizophrenia (Adler et al., 1982). Diminished inhibition has also been found in some unaffected relatives of persons with schizophrenia (Siegel et al., 1984; Clementz et al., 1998). Genetic linkage and association studies have used this physiological dysfunction as an endophenotype for schizophrenia. Association and linkage of diminished inhibition to polymorphisms in *CHRNA7*, the gene for $\alpha 7$ -nicotinic acetylcholine subunit, and *COMT*, the gene that produces catechol-o-methyltransferase, have been demonstrated with this phenotype (Freedman et al., 1997; Houy et al., 2004; Lu et al., 2007).

Diminished inhibition of the P50 component has been found by many laboratories worldwide, but there have also been failures to find differences. A meta-analysis of all available studies in 2004 showed a large effect size for the most common measure of P50 inhibition, the ratio of the amplitude of the second to the first response (Bramon et al., 2004). Although no evidence for heterogeneity was found, half the studies came from the University of Colorado and these studies showed a significantly larger effect size (de Wilde et al., 2007; Patterson et al., 2008). It was also noted that there were important differences between the Colorado protocols and those from laboratories that failed to find differences. The Colorado group uses a lower sound intensity, places subjects recumbent, and uses a beta to gamma electroencephalographic frequency bandpass filter (Griffith et al., 1995; Kisley et al., 2006). Thus, site differences and differences in technique were conflated.

A second issue is the selection of the optimal parameter to analyze the inhibition. The comparison of the responses to paired stimuli to assess inhibition is a classical neurophysiological technique. The paradigm is called conditioning and testing, because the first stimulus is hypothesized to excite target neurons as well as relevant inhibitory neurons, the latter either directly through feed forward circuits or indirectly through feedback circuits

from the target neurons. The conditioning or first stimulus thus elicits the response of the target neurons in the state when they are not inhibited and it also conditions or activates inhibitory circuits. The inhibitory circuits are not activated in time to affect the response to the conditioning stimulus. However, their inhibitory activity builds during the interstimulus interval (Miller et al., 1995). The second stimulus then tests the effect of these inhibitory circuits on the response of the target neurons.

For all inhibitory phenomena the question that arises is what parameter to use to compare the responses to the conditioning and test stimuli. In a simple neuronal circuit, the assumption is that the excitatory response to the conditioning stimulus is invariant. If that assumption is true, then any measure of comparison between the test and conditioning response, such as ratio or difference of amplitudes, is valid. In a complex human cerebral circuit, variance in the conditioning response is expected, because of differences in neurobiology, state of alertness, and drug effects. The ratio parameter is relatively robust to changes in medications, which affect the amplitude to both stimuli (Adler et al., 1989). However, the ratio parameter has been questioned because it becomes skewed by variation in the amplitude to the first stimulus, which is the denominator of the ratio (Smith et al., 1994; Anokhin et al., 2007). Persons with schizophrenia often have lower initial responses, and thus there may be some rationale for the difference parameter, even if it is more affected by medication.

The Consortium on the Genetics of Schizophrenia (COGS) was funded by the National Institute of Health to study the genetic liability of endophenotypes such as P50 inhibition. The Consortium is multi-site, which allows site differences in P50 recording data to be assessed. The acquisition of a large sample across the seven sites also meant that different parameters of the paradigm could be investigated for their ability to distinguish probands, relatives, and controls. We hypothesized that the specification of uniform recording methods would eliminate site differences and the both P50 ratio and difference would be significantly different between probands, relatives, and controls.

2. Methods

The Consortium on the Genetics of Schizophrenia encompasses sites at the University of California San Diego, University of California Los Angeles, University of Colorado Denver, Harvard University, Mount Sinai School of Medicine, University of Pennsylvania, and University of Washington. Institutional Review Boards at these sites and their affiliated institutions approved the study. All subjects provided informed consent to participate.

2.1. Subject Ascertainment and Diagnosis

Subjects were recruited from community settings and received the Diagnostic Interview for Genetic Studies and related instruments, as described in previous publications from the Consortium (Calkins et al., 2007). The 181 probands met DSM-IV criteria for schizophrenia; 156 were taking second generation antipsychotics, 7 were taking first generation antipsychotics, 9 were taking both, and 9 were taking no antipsychotic medication. Probands had to have at least one parents and one sibling who participated in the study. The community control comparison subjects had no personal or family history of psychosis or Cluster A personality disorder. Subjects in all groups were excluded for history of significant head injury or positive alcohol or drug urine toxicology screens on the day of assessment. Subjects were not allowed to smoke or use nicotine within 30 min of testing. The Scale for Assessment of Negative Symptoms and the Scale for Assessment of Positive Symptoms were completed as part of the assessment.

2.2. Cross-site training

All sites received identical equipment, an integrated auditory stimulator and amplifiers with custom software for acquisition, analogue filtering between 1 and 300 Hz, and 1 kHz digitization of data (LEA2003, RaveWave Systems, Aurora, CO). Testers participated in an initial joint training session, annual refresher sessions, and weekly teleconference. A quality assurance supervisor visited each site, which included observing recording and being recorded for comparison between sites.

2.3. Electrophysiological Recording

A 0.04 ms square wave was amplified from 20Hz-12kHz and delivered through earphones. The subject's threshold for this stimulus was determined in each ear, and the stimulus for each ear was set to 50dB above this threshold. Stimuli were paired with intra-pair interval 0.5 s and inter-pair interval 10 s.

Subjects sat semi-recumbent in a relaxation chair. They were instructed to remain awake and to fix their eyes on the wall 2 m across from the chair. Stimuli were delivered as 5 blocks of 20 stimulus pairs with 2 min rest between blocks. The testers, who were in the same room as the subject, were instructed to make sure that subjects stayed awake and alert, as judged by their appearance. The tester could observe if the electrical activity deviated by more than 50 μ V from baseline, a sign of likely startle or movement artifact, and then stop recording. Stimuli were reduced by 2 dB if such artifacts occurred.

The five blocks were averaged separately by an investigator blind to subject identity. Digital filtering was used to isolate activity between 10 and 100Hz. Averages which contained deflections greater than 50 μ V were excluded to prevent inclusion of movement artifacts and then a grand average was constructed. Final averages with conditioning P50 waves less than 1 μ V or electrooculographic potentials at 50 ms that were greater than the vertex potential were excluded.

The P50 wave was identified in a window 40 to 75 ms post conditioning stimulus and its amplitude measured relative to the first preceding negativity using the previously described computerized algorithm (Nagamoto et al., 1989). The test wave had to be within ± 10 ms of the latency from the test stimulus as the conditioning wave. Its amplitude was measured relative to its preceding negativity. This criterion reflects the 95% confidence limit for the latency variance between test and conditioning waves (Nagamoto et al., 1989). All recordings were reviewed by an investigator blind to subject identity for fidelity to this protocol.

2.4. Statistical analyses

Comparisons of the demographic variables were performed by Wilcoxon ranked sums test and Chi-square tests. A mixed model analysis of variance was used to assess group differences in P50 ratio (Proc MIXED, SAS version 9.1 software (SAS Institute Inc.: Cary, NC, 2004)). The model included a random family effect and separate covariance estimates for each of the three groups. Fixed factors of interest were group and research site. Covariates were age, sex, and education. There were no significant group by covariate interactions. Linear combinations of the least square means were used to test pairwise differences between groups. Admixture analyses were conducted using NOCOM (J. Ott, Rockefeller University, NY). The mean and standard deviations of the probands and controls were used as fixed parameters to detect possible admixture of the normal and affected phenotype in each group. The significance of the difference in ln-likelihood between a single distribution and a two-component distribution was tested by a Chi-square test.

3. Results

Recordings were completed and analyzed from 333 healthy community comparison controls, 181 probands with schizophrenia, and 429 of their first degree relatives. The proportion of analyzed recordings, after exclusion of recordings with artifacts, ranged from 66% to 77% from each site, mean $71\% \pm 3\%$ (s.d.), and was not significantly different across sites. The proportion of analyzed recordings was also similar across the three subject groups: 74% in the controls, compared to 69% in both the probands with schizophrenia and their relatives. Table 1 shows demographic variables. Relatives were significantly older because of the inclusion of parents. Probands were less likely to be female, had less education, and were more likely to smoke.

3.1. Differences in physiological parameters between groups

Significant differences were found between groups for P50 ratio in a mixed model analysis of variance that included group, site, years of education, gender, age, and smoking status as fixed variables and family as a random variable. There was a significant effect for group ($F = 20.82$, $df\ 2, 760$, $P < 0.0001$). The estimated P50 ratio least square mean for controls was 0.37 ± 0.02 (s.e.). For probands it was 0.62 ± 0.04 (s.e.), and for relatives it was 0.49 ± 0.02 (s.e.). The comparison of controls and probands was highly significant ($t = 5.75$, $df\ 760$, $P < 0.0001$). The controls also differed from the relatives ($t = 4.54$, $df\ 760$, $P = 0.0003$). The probands and relatives were less significantly different ($t = 2.52$, $df\ 760$, $P = 0.01$).

Analysis of variance for each component of the response showed a modest effect of group for conditioning amplitude ($F = 3.80$, $df\ 2, 760$, $P = 0.02$) and a more significant effect for test amplitude ($F = 7.94$, $df\ 2, 760$, $P = 0.0004$). The difference between the components (conditioning amplitude – test amplitude) also showed a significant group effect ($F = 16.14$, $df\ 2, 760$, $P < 0.0001$). Means and standard deviations for all parameters are shown in Table 2.

The effect size for distinguishing P50 parameters in schizophrenia from the controls was 0.57 for the ratio of the amplitudes, 0.49 for their difference, 0.23 for the conditioning amplitude alone, and 0.32 for the test amplitude alone. Pearson's correlations were performed to explore relationships between these parameters. The conditioning and the test amplitude were themselves correlated with each other ($r = 0.61$).

The ratio of the amplitudes was correlated with the difference between the amplitudes ($r = -0.64$). The conditioning amplitude was marginally correlated with the ratio of the amplitudes ($r = -0.14$), whereas it was more highly correlated with the difference between the amplitudes ($r = 0.77$). The test amplitude was more highly correlated with the ratio of the amplitudes ($r = 0.58$) than with their difference ($r = -0.03$).

There were no significant correlations between P50 parameters and clinical ratings.

3.2. Evidence for admixture of the physiological deficit in families with schizophrenia

Both the difference and ratio parameters are significantly different in first degree relatives compared to controls, and both parameters have values that are approximately halfway between the values for the probands and the controls, consistent with the relatives' predicted sharing of 50% of any abnormal genes related to schizophrenia. However, the distributions of individual values in the three groups are quite different for the two parameters. For the ratio of amplitudes, the controls formed an apparently homogeneous group. The probands could be divided into two groups by the admixture analysis, with the group resembling controls comprising 39% of the probands and the other 61% in a higher range (Chi-square = 12.4, $df\ 1$, $P = 0.0004$). Among the first degree relatives, 63% resembled the controls and

37% resembled the probands (Chi-square = 13.0, df 1, $P = 0.0003$). Figure 1 is a histogram of values for all three groups, with the distributions derived from admixture analysis. The difference parameter was homogeneous in all three groups, with no significant evidence for admixture.

The parents ($N = 139$) were compared with the siblings ($N = 289$). The two groups did not differ on P50 ratio (0.50 ± 0.39 (s.d.) for parents and 0.50 ± 0.32 for siblings) or the difference between P50 amplitudes (1.51 ± 1.3 for parents and 1.72 ± 1.5 for siblings).

4. Discussion

The Consortium on Genetics of Schizophrenia is the largest single study of the P50 auditory evoked potential ever conducted in controls, probands, and relatives. Other papers from the Consortium will analyze the inter-relationship between this test and other tests of sensory gating dysfunction and cognition. The purpose of this paper is to examine the measure itself. A significant difference between probands and community comparison controls was observed in both the ratio of the amplitudes to the two stimuli and their difference, with first degree relatives in an intermediate position. No site effects were found, likely because comparable protocols and equipment and cross-site training and quality control were utilized, as they were for all Consortium phenotyping efforts.

4.1. Factors influencing inhibition of response

The recordings were conducted within a battery of demanding neurocognitive and physiological tests. Demands on the subjects' concentration and patience contribute to increased adrenergic tone, which has been correlated with diminished inhibition of the P50 response, likely because cerebral inhibitory neurons are inhibited by norepinephrine (Madison and Nichol, 1988). In other studies, increased levels of adrenergic metabolites correlated with diminished P50 inhibition (Waldo et al., 1992). P50 inhibition has been recorded in desynchronized sleep, when noradrenergic neurotransmission ceases; a mean ratio of 0.15 in control subjects was observed (Kisely et al., 2001, 2003). This difference between the usual waking state and a state without noradrenergic tone suggests that efforts to calm subjects to decrease noradrenergic tone should be increased to eliminate this source of variance as much as possible.

The subjects were recorded semi-recumbent in a relaxation chair, rather than fully recumbent. This decision resulted in less sleepiness as assessed by fewer recordings with prominent alpha and delta EEG waves, a frequent contributor to failure to observe normal P50 inhibition. However, it may have also increased eye movements in response to the stimuli. We did not analyze recordings in which the potential recorded in electro-oculographic electrodes exceeded the electroencephalographic potential recorded at the vertex. Although algorithms using regression techniques are frequently used to separate the electroencephalographic and electro-oculographic activities, cerebral activity in response to sound is increased during eye movements and inhibition of the P50 response is lost. When eye movements are elicited, the brain is responding with attentional mechanisms that inactivate inhibitory sensory gating mechanisms that would otherwise prevent response (Sobotka et al., 1997). Hence very loud sounds, which elicit eye movements or startle, do not elicit inhibition of P50 responses. In this study, we therefore employed sounds in a limited range, 50dB above the subject's hearing threshold (Griffith et al., 1995). In some cases, this sound level may actually have been inadequate to elicit a P50 response reliably. To preserve blinding of the recording technician, we decided not to perform online processing of the electroencephalographic activity during the recording. All artifact rejection and averaging was performed later by an investigator who was blind to subject identity. However, this decision meant that some recordings were not suitable for analysis because

either eye movements occurred in response to the sound, which might have been avoided by slight adjustments downward in volume, or the P50 response to the first sound was less than 1 μ V, the pre-established criterion for reliable measurement, which might have been avoided by slight adjustments upward in volume. Nonetheless, the rate of rejection of recordings was similar across groups and sites and was therefore not a source of bias.

The dysfunction of cerebral inhibition as measured by P50 inhibition in the probands in this study was less marked than we have earlier observed, perhaps because nearly 90% of them were on second generation neuroleptics, many of which have been found to partially ameliorate the P50 inhibitory deficit (Adler et al., 2004). The admixture analysis in the probands supports this hypothesis, with 40% having values more typical of controls.

The lack of relationship of P50 inhibition to clinical measures is consistent with other studies that show no change in P50 inhibition as clinical ratings change with treatment in schizophrenia (Hong et al., 2009).

4.2. Rationale for alternative measurements of cerebral inhibition

The large data set made possible the examination of two different strategies for analyzing the effects of inhibitory neuronal function in this paradigm. Both strategies, the calculation of ratios and differences between the amplitudes, produced highly significant mean differences between controls and probands, as would be expected because both are valid means to examine inhibition of the response to the second stimulus. Nonetheless, neither is a direct measure of the activity of inhibitory neuronal circuits and thus both are confounded by a possible relationship to other neuronal circuits, including those responsible for the control of excitation. In this experiment, we observed that the two measures are related to each other.

The ratio parameter is more closely related to the amplitude of the test wave than the difference parameter. This parameter has been shown to be related to hemodynamic activity in the hippocampus, thalamus, and dorsal lateral prefrontal cortex when subjects are listening to repeated sounds during functional magnetic resonance imaging (Tregellas et al., 2007). The difference measure has not yet been evaluated neurobiologically.

Both parameters of P50 inhibition have been used in genetic studies. Both show evidence for heritability in twin studies and, within these studies, the ratio is related to the risk for schizophrenia (Hall et al., 2006; Anokhin et al., 2007). Some consideration might be given to the genetic model in choosing which parameter to use. In this study, the ratio and difference parameters had different distributions of individuals, particularly among the relatives. These distributions are the first steps of genetic analysis, in accordance with Mendel's first law of the segregation of characteristics. To the extent that there is a major gene effect, P50 ratio would seem to be a good choice as it shows evidence for segregation, which is expected when there is a major gene effect, and it has been successfully used in linkage and association studies to show effects (Freedman et al., 1997). However, the ratio did not show significant heritability in the initial Consortium on Genetics of Schizophrenia heritability analysis of a subset of the subjects from this study, which used a variance component method that is most compatible with multigenic effects (Greenwood et al., 2007). Here, the difference measure showed significant results. Its lack of apparent segregation gives it a more normal distribution, which is helpful for variance component analysis.

4.3 Conclusion

Inhibition of the P50 auditory evoked response showed significant differences between schizophrenia probands and controls across multiples sites in the COGS collaboration,

analyzed as both the ratio and difference of amplitudes of the responses to paired auditory stimuli. Admixture analyses P50 inhibition in probands, controls, and first degree relatives were consistent with the segregation of a genetically based endophenotype.

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References

- Adler LE, Gerhardt GA, Franks R, Baker N, Nagamoto H, Drebing C, Freedman R. Sensory physiology and catecholamines in schizophrenia and mania. *Psychiatry Res.* 1989; 31:297–309. [PubMed: 2333360]
- Adler LE, Olincy A, Cawthra E, McRae K, Harris J, Nagamoto H, Waldo MC, Hall M, Ross R, Freedman R. The varied effects of atypical medications on P50 auditory gating in schizophrenic patients. *Am J Psychiatry.* 2004; 161:1822–1828. [PubMed: 15465979]
- Adler LE, Pachtman E, Franks R, Freedman R. Neurophysiologic evidence for a defect in neuronal mechanisms involved in sensory gating in schizophrenia. *Biol Psych.* 1982; 17:639–654.
- Anokhin AP, Vedeniapin AB, Heath AC, Korzyukov O, Boutros NN. Genetic and environmental influences on sensory gating of mid-latency auditory evoked responses: a twin study. *Schizophrenia Res.* 2007; 89(1-3):312–9.
- Bramon E, Rabe-Hesketh S, Sham P, Murray RM, Frangou S. Meta-analysis of the P300 and P50 waveforms in schizophrenia. *Schizophrenia Res.* 2004; 70(2-3):315–329.
- Calkins ME, Dobie DJ, Cadenhead KS, Olincy A, Freedman R, Green MF, Greenwood TA, Gur RE, Gur RC, Light GA, Mintz J, Nuechterlein KH, Radant AD, Schork NJ, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Braff DL. The Consortium on the Genetics of Endophenotypes in Schizophrenia, Model Recruitment, Assessment, and Endophenotyping Methods for a Multisite Collaboration. *Schizophrenia Bulletin.* 2007; 33:33–48. [PubMed: 17035358]
- Clementz BA, Geyer MA, Braff DL. Poor P50 suppression among schizophrenia patients and their first-degree relatives. *Am J Psychiatry.* 1998; 155:1691–1694. [PubMed: 9842777]
- de Wilde OM, Bour LJ, Dingemans PM, Koelman JH, Linszen DH. A meta-analysis of P50 studies in patients with schizophrenia and relatives: differences in methodology between research groups. *Schizophrenia Research.* 2007; 97(1-3):137–151. [PubMed: 17604606]
- Erwin RJ, Mawhinney-Hee M, Gur RC, Gur RE. Midlatency auditory evoked response in schizophrenia. *Biol Psychiatry.* 1991; 30:430–442. [PubMed: 1932393]
- Freedman R, Coon H, Myles-Worsley M, Orr-Urtreger A, Olincy A, Davis A, Polymeropoulos M, Holik J, Hopkins J, Hoff M, Rosenthal J, Waldo MC, Reimherr F, Wender P, Yaw J, Young DA, Breese CR, Adams C, Patterson D, Adler LE, Kruglyak L, Leonard S, Byerley W. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. *Proc Natl Acad Sci U S A.* 1997; 94:587–592. [PubMed: 9012828]
- Greenwood TA, Braff DL, Light GA, Cadenhead KS, Calkins ME, Dobie DJ, Freedman R, Green MF, Gur RE, Gur RC, Mintz J, Nuechterlein KH, Olincy A, Radant AD, Seidman LJ, Siever LJ, Silverman JM, Stone WS, Swerdlow NR, Tsuang DW, Tsuang MT, Turetsky BI, Schork NJ. Initial heritability analyses of endophenotypic measures for schizophrenia: the consortium on the genetics of schizophrenia. *Arch Gen Psychiatry.* 2007; 64(11):1242–1250. [PubMed: 17984393]
- Griffith J, Hoffer LD, Adler LE, Zerbe GO, Freedman R. Effects of sound intensity on a midlatency evoked response to repeated auditory stimuli in schizophrenic and normal subjects. *Psychophysiol.* 1995; 32:460–466.

- Hall MH, Schulze K, Rijdsdijk F, Picchioni M, Ettinger U, Bramon E, Freedman R, Murray RM, Sham P. Heritability and Reliability of P300, P50 and Duration Mismatch Negativity. *Behavioral Genetics*. 2006; 36:845–857.
- Hong X, Chan RCK, Zhuang X, Jiang T, Wan X, Wang J, Xiao B, Zhou H, Jiuang L, Weng B. Neuroleptic effects on P50 sensory gating in patients with first-episode never-medicated schizophrenia. *Schizophrenia Res*. 2009; 108:151–157.
- Houy E, Raux G, Thibaut F, Belmont A, Demily C, Allio G, Haouzir S, Fouldrin G, Petit M, Frebourg T. The promoter –194 C polymorphism of the nicotinic alpha 7 receptor gene has a protective effect against the P50 sensory gating deficit. *Mol Psychiatry*. 2004; 9:320–322. [PubMed: 14569275]
- Kisley MA, Cornwell ZM. Gamma and beta neural activity evoked during a sensory gating paradigm: effects of auditory, somatosensory and cross-modal stimulation. *Clinical Neurophysiology*. 2006; 117(11):2549–2563. [PubMed: 17008125]
- Kisley MA, Olincy A, Freedman R. The effect of state on sensory gating: comparison of waking, REM and non-REM sleep. *Clinical Neurophysiology*. 2001; 112:1154–1165. [PubMed: 11516727]
- Kisley MA, Olincy A, Robbins E, Polk SD, Adler LE, Waldo MC, Freedman R. Sensory gating impairment associated with schizophrenia persists into REM sleep. *Psychophysiology*. 2003; 40:29–38. [PubMed: 12751801]
- Leonard S, Gault J, Hopkins J, Logel J, Vianzon R, Short M, Drebing C, Berger R, Venn D, Sirota P, Zerbe G, Olincy A, Ross RG, Adler LE, Freedman R. Promoter variants in the $\alpha 7$ nicotinic acetylcholine receptor subunit gene are associated with an inhibitory deficit found in schizophrenia. *Arch Gen Psychiatry*. 2002; 59:1085–1090. [PubMed: 12470124]
- Light GA, Geyer MA, Clementz BA, Cadenhead KS, Braff DL. Normal P50 suppression in schizophrenia in patients treated with atypical antipsychotic medications. *Am J Psychiatry*. 2000; 157:767–771. [PubMed: 10784470]
- Lu BY, Martin KE, Edgar JC, Smith AK, Lewis SF, Escamilla MA, Miller GA, Canive JM. Effect of catechol O-methyltransferase val(158)met polymorphism on the p50 gating endophenotype in schizophrenia. *Biol Psychiatry*. 2007; 62(7):822–825. [PubMed: 17448448]
- Madison DV, Nicoll RA. Norepinephrine decreases synaptic inhibition in the rat hippocampus. *Brain Research*. 1988; 442(1):131–118. [PubMed: 2834010]
- Miller CC, Freedman R. The activity of hippocampal interneurons and pyramidal cells during the response of the hippocampus to repeated auditory stimuli. *Neurosci*. 1995; 69:371–381.
- Nagamoto HT, Adler LE, Waldo MC, Freedman R. Sensory gating in schizophrenics and normal controls. Effects of changing stimulation interval. *Biol Psychiatry*. 1989; 25:549–561. [PubMed: 2920190]
- Patterson JV, Hetrick WP, Boutros NN, Jin Y, Sandman C, Stern H, Potkin S, Bunney WE Jr. P50 sensory gating ratios in schizophrenics and controls: a review and data analysis. *Psychiatry Research*. 2008; 158(2):226–247. [PubMed: 18187207]
- Siegel C, Waldo M, Mizner G, Adler LE, Freedman R. Deficits in sensory gating in schizophrenic patients and their relatives. *Arch Gen Psychiatry*. 1984; 41:607–612. [PubMed: 6732421]
- Smith DA, Boutros NN, Schwatzkopf SB. Reliability of P50 auditory event-related potential indices of sensory gating. *Psychophysiology*. 1994; 31:607–612.
- Sobotka S, Nowicka A, Ringo JL. Activity linked to externally cued saccades in single units recorded from hippocampal, parahippocampal, and inferotemporal areas of macaques. *J Neurophysiol*. 1997; 78:2156–2163. [PubMed: 9325382]
- Tregellas JR, Davalos DB, Rojas DC, Waldo MC, Gibson L, Wylie K, Du YP, Freedman R. Increased hemodynamic response in the hippocampus, thalamus and prefrontal cortex during abnormal sensory gating in schizophrenia. *Schizophrenia Res*. 2007; 92:262–272.
- Waldo, Gerhardt G, Baker N, Drebing C, Cawthra E, Freedman R. Auditory sensory gating and catecholamine metabolism in schizophrenic and normal subjects. *Psychiatry Res*. 1992; 44:21–32. [PubMed: 1461944]

Figure 1.

Auditory evoked responses as recorded at the vertex (EEG) and near the eye (EOG) in response to paired auditory stimuli (arrowheads) from a control subject and from a schizophrenia proband. The P50 was identified by a computer algorithm and measured relative to the preceding negativity (Nagamoto et al., 1989). The ratio of P50 amplitudes for the control subject was 0.31; the difference was 3.1 μV . The ratio of P50 amplitudes for the schizophrenia proband was 0.62; the difference was 1.6 μV .

Figure 2.

Histogram (dots) and admixture analysis of the ratio of the test to conditioning P50 amplitude in community comparison controls, probands with schizophrenia, and their first degree relatives. The dashed line is the distribution based on the mean and standard deviation of the controls and the solid line is the distribution based on the mean and standard deviation of the probands. A significant admixture was detected in the probands and relatives.

Table 1
Demographic variables in the community comparison control subjects, probands with schizophrenia, and their first degree relatives

Group	Age (median yrs) ^a 25-75 %ile)	Female (%) ^a	European (%)	Education (median yrs) ^a (25-75%ile)	Smoking (%) ^a
Community comparison controls	32 25-47	59	53	16 14-16	14
Probands	32 25-42	24	56	13 12-15	45
First degree relatives	46 30-55	58	64	16 14-17	15

^a $P < 0.01$ from comparison between groups by Wilcoxon ranked sums test for age and education and by Chi-square for gender, ethnicity, and smoking status.

Table 2

P50 amplitudes in response to paired auditory stimuli

Group	Condition amplitude ¹ (μ V)		Test amplitude ² (μ V)		Ratio of amplitudes ³		Difference between amplitudes ⁴ (μ V)	
	mean	s.d.	mean	s.d.	mean	s.d.	mean	s.d.
Community comparison controls	3.17	1.78	1.16	0.99	0.38	0.32	2.01	1.48
Probands	2.77	1.57	1.47	1.20	0.60	0.48	1.26	1.48
First degree relatives	3.14	2.03	1.48	1.28	0.50	0.35	1.64	1.43