

Neurophysiological Endophenotypes of Schizophrenia: The Viability of Selected Candidate Measures

Bruce I. Turetsky^{1,2}, Monica E. Calkins², Gregory A. Light³, Ann Olincy⁴, Allen D. Radant⁵, and Neal R. Swerdlow³

²Department of Psychiatry, 10th floor, Gates Building, University of Pennsylvania, 3400 Spruce Street, Philadelphia, PA 19104;

³Department of Psychiatry, University of California San Diego, La Jolla, CA; ⁴Department of Psychiatry, University of Colorado Health Sciences Center, Denver, CO; ⁵Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, WA

In an effort to reveal susceptibility genes, schizophrenia research has turned to the endophenotype strategy. Endophenotypes are characteristics that reflect the actions of genes predisposing an individual to a disorder, even in the absence of diagnosable pathology. Individual endophenotypes are presumably determined by fewer genes than the more complex phenotype of schizophrenia and would, therefore, reduce the complexity of genetic analyses. Unfortunately, despite there being rational criteria to define a viable endophenotype, the term is sometimes applied indiscriminately to characteristics that are deviant in affected individuals. Schizophrenia patients exhibit deficits in several neurophysiological measures of information processing that have been proposed as candidate endophenotypes. Successful processing of sensory inputs requires the ability to inhibit intrinsic responses to redundant stimuli and, reciprocally, to facilitate responses to less frequent salient stimuli. There is evidence to suggest that both these processes are “impaired” in schizophrenia. Measures of inhibitory failure include prepulse inhibition of the startle reflex, P50 auditory evoked potential suppression, and antisaccade eye movements. Measures of impaired deviance detection include mismatch negativity and the P300 event-related potential. The purpose of this review is to systematically evaluate the endophenotype candidacy of these key neurophysiological abilities. For each candidate, we describe typical experimental procedures, the current understanding of the underlying neurobiology, the nature of the abnormality in schizophrenia, the reliability, stability and heritability of the measure, and any reported gene associations. We con-

clude with a discussion of the few studies thus far that have employed a multivariate approach with these candidates.

Keywords: prepulse inhibition/P50/antisaccade/mismatch negativity/P300/ERP

Introduction

In an effort to finally reveal susceptibility genes ensconced in the human genome, schizophrenia research has turned, at a remarkable pace, to the endophenotype strategy. Endophenotypes are characteristics, usually assessed in a laboratory, that reflect the actions of genes predisposing an individual to a specific disorder, even in the absence of any diagnosable pathology. As relatively simple, well-defined and quantifiable biobehavioral characteristics, individual endophenotypes are presumably determined by fewer genes than the more complex phenotype of schizophrenia. Ideally, therefore, endophenotypes could serve as dissected components of the complex schizophrenia phenotype, reflecting fewer genes and thereby reducing the complexity of the genetic analyses required to identify contributing genes.

Investigations of endophenotypes of psychopathology have accelerated because of a growing recognition of the promise of the approach, as described by Gottesman and Gould¹ in their influential and oft-cited discussion of the strategy. At the time of their report, a MEDLINE search for “endophenotype” identified 62 entries between the years 2000 and 2002, compared with 16 articles prior to 2000. For 2003 through June 2006, an additional 109 publications with keyword endophenotype have been added to MEDLINE, reflecting a substantial increase over all prior years. The psychopathology research field is now abuzz with the endophenotype term. Unfortunately, the term is sometimes applied indiscriminately to any characteristic observed to be “deviant” in affected individuals. There is a risk, with the science striving to advance so quickly, that the rigorous critical evaluation of candidate endophenotypes will fall to the wayside. There are several criteria, rationally stemming from their proposed use as tools for revealing the genetic and neurobiological underpinnings of psychopathology, that

¹To whom correspondence should be addressed; tel: 215-615-3607, fax: 215-662-7903, e-mail: turetsky@bbl.med.upenn.edu.

candidate measures should meet, if they are to be considered viable endophenotypes.¹⁻⁴ While there is some variability in specific criteria, it is generally agreed that the ideal candidate endophenotype would exhibit the following features:

1. It is associated with a disorder and represents a robust impairment that is stable and reproducible in an individual subject, with high test-retest reliability and state independence.
2. It is highly heritable, so that intra- and interfamilial variance could be attributed to shared genetic, rather than environmental, factors.
3. It cosegregates with illness within families but is also evident in unaffected members.
4. In growing recognition of the necessity of large samples for well-powered analyses, the candidate's measurement should be rapid and easy, so that it can be readily acquired in large numbers of patients with minimal subject cooperation or effort.
5. It reflects a discrete and well-understood neurobiological mechanism that is both informative for the pathophysiology of a disorder and indicative of the action of a limited number of genes.

Individual endophenotypes fulfilling these criteria may constitute independent risk factors that identify different unrelated types of genetic risk. Conversely, if multiple deficits tend to coaggregate in the families of patients with a specific disorder, it would suggest that the combined set of deficits reflect a single, common variant of genetic risk for the disorder. An alternative to the use of a single endophenotype is to combine endophenotypes or create a composite, multivariate endophenotype, in order to better identify genetic risk.⁵⁻⁷ Although there is a growing interest in the investigation of multivariate endophenotypes,⁷⁻¹⁰ most research to date has centered on the evaluation of individual candidate endophenotypes.

If individual candidates are to form a multivariate endophenotype, it is arguably important that each candidate stand alone as a viable endophenotype. Schizophrenia patients exhibit well-documented deficits in several laboratory-assessed neurophysiological abilities that have been proposed as candidate endophenotypes. Observed deficits extend from the earliest preattentive stages of information processing to relatively late higher cortical processes. However, it has been suggested that a breakdown in the processes that regulate the inflow of information from the environment is fundamental.¹¹ Successful processing of sensory inputs requires the ability to screen out or inhibit intrinsic responses to redundant or irrelevant inputs and, reciprocally, to enhance or facilitate responses to deviant, novel, or salient stimuli. There is evidence to suggest that both these discrete but related processes are "impaired" in schizophrenia. Among measures of inhibitory failure, those most commonly studied

in schizophrenia are prepulse inhibition (PPI) of the startle reflex, P50 auditory evoked potential suppression, and AS eye movements. Among measures of impaired deviance detection, mismatch negativity (MMN) and the P300 event-related potential (ERP) have been most commonly studied. While there have been reviews of particular aspects of the literature related to the endophenotype candidacy of each of these neurophysiological measures,^{12,13} to our knowledge, there have been no reviews describing how well each individual candidate fulfills all the above criteria.

The primary purpose of the current review is, therefore, to offer a systematic evaluation of the endophenotype candidacy of the key neurophysiological abilities implicated in schizophrenia. For each candidate, we describe typical experimental procedures, current understanding of the underlying neurobiology, the nature of the abnormality in schizophrenia, the reliability, stability and heritability of the measure, and any reported specific gene associations. As a reflection of the current state of the field, we first review the extensive literature on each individual candidate endophenotype. We then conclude with a discussion of the few studies thus far that have employed a multivariate approach with these candidates.

Measures of Inhibitory Failure

Prepulse Inhibition of Startle

PPI is the normal reduction in startle that occurs when a startling stimulus is preceded 30–300 ms by a weak prestimulus.¹⁴ PPI is deficient in schizophrenia patients and unaffected relatives,¹⁵⁻¹⁹ suggesting that it may be a trait marker for individuals at risk for developing the disorder (rather than a marker of schizophrenia per se).

Experimental Procedures. The assessment of PPI requires appropriate stimulus delivery time-locked to the acquisition of a valid measure of startle response magnitude. Though startle can also be elicited via a robust, abrupt visual, or tactile (air puff or electrical) stimulus, acoustic stimuli allow a high degree of experimental control and precision, and avoid logistical complexities of delivering electrical shocks to acutely psychotic individuals. The motor response most often used to assess startle and PPI in humans is the contraction of orbicularis oculi (OO) via electromyographic (EMG) measures during the first 250-ms epoch after startle stimulus onset.

There are many variants of startle/PPI acquisition procedures. For one common test procedure, subjects sit in a comfortable chair in a sound-attenuated room with a constant, neutral visual field (because any weak "noise" or visual stimulus can serve as a prepulse). Because of potential lateralized differences in the neural regulation of PPI, and its deficits in clinical populations,¹⁶ bilateral

eyeblink measures are optimal. EMG electrodes are positioned below and lateral to each eye over OO, with a ground electrode behind one ear. Common blink acquisition and scoring parameters are described elsewhere.²⁰ Startle stimuli are most commonly presented binaurally through headphones. Importantly, most studies reporting PPI deficits in schizophrenia populations use an “uninstructed” test session, in which test subjects are informed that they will hear noises, but are not instructed to perform any task related to those noises, that might engage volitional or attentional mechanisms.¹⁹

Stimulus parameters and test session design are selected based on the specific experimental questions of highest priority. Typically, in our studies, a test session includes a total of 74 active and 18 blank “no-stim” trials, and lasts 23.5 minutes, beginning with a 5-minute acclimation period with 70-dB (A) sound pressure level (SPL) white noise that continues throughout the session. Startle stimuli are 40-ms 115-dB (A) SPL noise bursts. Prepulses are discrete 20-ms noise bursts 15 dB above background, with onset 30, 60, or 120 ms prior to pulse onset. Figure 1

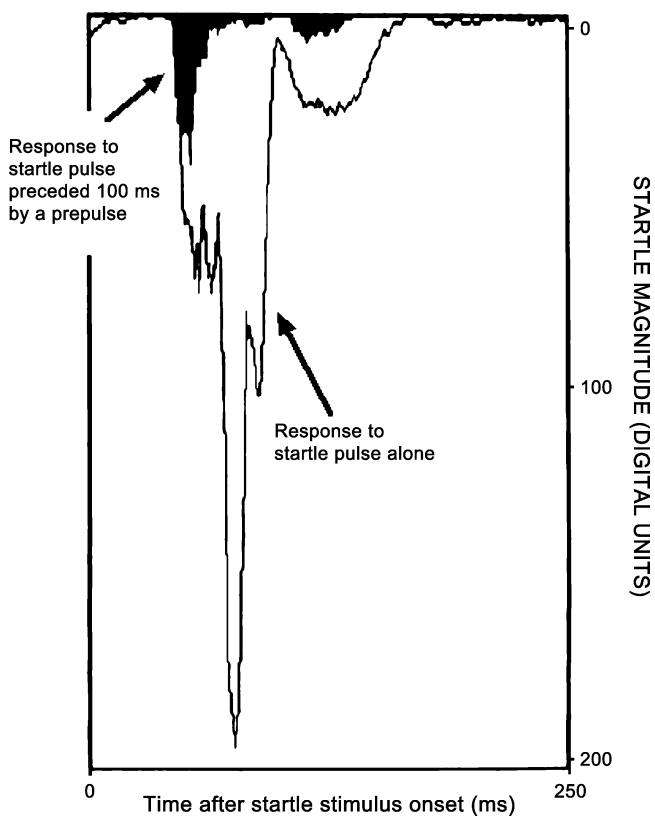


Fig. 1. The acoustic startle response to 110-dB SPL white noise burst, recorded from EMG electrodes situated over the OO muscle. The magnitude of the startle response is reduced when the startle pulse is preceded by a lower intensity auditory prepulse. In this example, an 85-dB white noise prepulse was presented 100 ms prior to the startle stimulus. Schizophrenia patients typically exhibit less attenuation of the acoustic startle response following the prepulse.

illustrates the effect of a prepulse on the magnitude of the startle response.

Neurobiology of PPI. Preclinical studies have demonstrated that PPI in rodents is regulated by cortical structures (mesial temporal cortex and medial prefrontal cortex [PFC]) and subcortical structures (striatum, pallidum, and pontine tegmentum).²¹ This limbic cortico-striato-pallido-pontine circuitry converges with the primary startle circuit at the level of the nucleus reticularis pontis caudalis (NRPC).

Studies of the neurobiology of PPI in humans reveal both similarities and differences from findings in animal models. For example, evidence of profound PPI deficits in patients with Huntington disease (HD)^{22,23} support the role of the striatum in the regulation of PPI in humans and parallel findings of PPI deficits after excitotoxic lesions of the striatum in rats and in mice transgenic for the HD gene.^{24,25} Neuroimaging studies in schizophrenia patients and normal comparison subjects confirm both the role of limbic cortico-striato-pallido-thalamic (CSPT) circuitry in the normal regulation of PPI^{21,26} and the association between CSPT abnormalities and PPI deficits in patients. Also consistent with a number of preclinical findings is the fact that PPI deficits are observed in other clinical populations, ranging from Tourette syndrome to seizure disorders, with known or presumed pathology in limbic CSPT circuitry.¹⁹

On the other hand, pharmacological studies of PPI in normal humans raise questions as to whether the PPI neural circuit “blueprint” in rodents can be easily translated across species.^{21,27} Thus, while the indirect dopamine (DA) agonist, *D*-amphetamine, reduces PPI in both normal humans and some rodent strains, the *N*-methyl-*D*-aspartate (NMDA) antagonist ketamine, and the serotonin releaser methylene-dioxy-methamphetamine have opposite effects on PPI across species—disrupting PPI in rodents but increasing PPI in clinically normal humans. A similar pattern is observed with the mixed DA agonist/NMDA antagonist amantadine. Direct DA agonists potently disrupt PPI in rats, but their effects in humans are not as convincing. Both atypical antipsychotics and nicotine have been reported to increase PPI across species but perhaps only under certain experimental conditions.

Abnormality in schizophrenia. Schizophrenia patients exhibit abnormal PPI despite having relatively normal responses to startling stimuli, as indicated by measures of startle amplitude, latency, and latency facilitation. Empirically, these PPI deficits indicate that in the immediate aftermath of a stimulus, the central nervous system in schizophrenia is overly responsive to a second stimulus. Conceptually, this deficit of time-locked, automatic inhibition puts the information contained in the initial stimulus at greater risk of being degraded, thereby disrupting its appropriate cognitive or behavioral impact.

Importantly, there is no direct evidence that the sensory processing of the prepulse is degraded in patients nor is there direct evidence that this presumed degradation of prepulse processing causes impairments in the cognitive functions that depend on the intact sensory processing of the prepulse. However, PPI deficits in schizophrenia patients are not modality specific,²⁰ and they correlate with distractibility²⁸ and thought disorder^{29,30} measures and more global scales of functioning.³¹

Reliability. Some forms of PPI exhibit robust test-test reliability in normal comparison subjects, over intervals of several months.^{32,33} Thus, intraclass correlations exceeding 0.90 have been observed for PPI elicited over 3 consecutive months, using relatively intense prepulses³⁴ and 30- to 120-ms prepulse intervals. With shorter prepulse intervals, and/or weaker prepulse intensities, PPI is less reliable over time.^{34,35}

Stability. Relatively few studies have assessed the longitudinal stability of PPI deficits in schizophrenia patients. While PPI deficits have been reported by several groups in relatively stable, medicated schizophrenia cohorts,^{16,19,36-40} others report that PPI deficits occur only in patients who are in an acute symptomatic phase of a psychotic episode and resolve in these same patients as symptoms subside.⁴¹ One complexity in interpreting such “state-related” changes in PPI relates to the role of antipsychotic medications in both symptomatic improvement and potentiation of PPI (see below).

Heritability. Very convincing evidence for the genetic control of PPI comes from studies in rodents. For example, Francis *et al.*⁴² reported that mice generated via embryonic transplants into a different maternal strain exhibited PPI phenotypes of the embryo and not of the maternal uterine or rearing environments. Thus, PPI appears to be linked closely to genotype in mice. PPI levels differ substantially across mouse strains,⁴³ and strain-specific PPI phenotypes are stable over multiple generations. One published study has directly assessed heritability of PPI in humans. Anokhin *et al.*⁴⁴ assessed PPI in 40 monozygotic (MZ) and 31 dizygotic (DZ) female twin pairs and used structural equation modeling to demonstrate heritability that accounted for over 50% of PPI variance. Menstrual cycle phase was not matched in these twin pairs, suggesting that heritability may have actually been higher, given the likely added variance in this sample based on the differential hormonal “state” influences on PPI (see below).^{45,46}

Cadenhead *et al.*¹⁶ reported PPI deficits in first-degree relatives of schizophrenia probands. Preliminary analyses¹⁷ using an “impaired” criterion of PPI (>1 SD below control means) revealed an “impaired PPI” status in 8/12 unaffected siblings of schizophrenia probands vs 5/25 controls ($P < .005$); analyses using impaired schizophre-

nia probands and their unaffected siblings revealed a relative risk of impaired PPI of 3.13. Pearson correlation between sib-pairs was .66. This finding of impaired PPI in unaffected siblings of schizophrenia patients was recently replicated by Kumari *et al.*¹⁸ in larger samples. Preliminary analysis of the Consortium on the Genetics of Schizophrenia (COGS) data sample, for 284 individuals, found PPI heritability to be significant at 0.24 ($P < .05$) (T. A. Greenwood, D. L. Braff, K. S. Cadenhead, M. E. Calkins, D. J. Dobie, R. Freedman, M. F. Green, R. E. Gur, R. C. Gur, G. A. Light, J. Mintz, K. H. Nuechterlein, A. Olincy, A. D. Radant, L. J. Seidman, L. J. Siever, J. M. Silverman, W. S. Stone, N. R. Swerdlow, D. W. Tsuang, M. T. Tsuang, B. I. Turetsky, N. J. Schork unpublished data).

Other Factors Influencing Endophenotype Utility.
Antipsychotics. The initial report of PPI deficits in schizophrenia patients¹⁵ predated the use of atypical antipsychotics. Subsequent clinical reports have suggested that atypical antipsychotics are associated with greater and potentially “normalized” PPI levels in schizophrenia patients.^{19,31,40,41,47} Because an overwhelming number of schizophrenia patients are currently treated with atypical antipsychotics, it is possible that PPI deficits in this population are a “vanishing” biomarker. Alternative strategies for understanding the biology and clinical implications of deficient sensorimotor gating have become increasingly important, including the use of “optimized” stimulus features (eg, 60-ms prepulse intervals),⁴⁸ broadband stimuli and prominent background noise,⁴⁹ unmedicated schizophrenia^{41,50} and schizophrenia “spectrum” patients,^{16,51} unaffected family members, and populations of “low-gating” controls.⁴⁸

Nicotine. “Progating” effects of nicotine have been reported in measures of both PPI and P50 ERP suppression.^{19,52-54} If nicotine use per se is associated with increased PPI, then the higher rates of smoking among schizophrenia patients would be expected to diminish patient vs control group differences in PPI measures and to diminish measures of heritability.

Sex Differences. Sex differences and menstrual cyclicity in PPI have been reported by several different groups^{45,46,55-58} and may have important implications for the interpretation of PPI differences in schizophrenia vs control populations. Typically, “open” subject recruitment in studies favors ascertainment of male patients and female controls. Because men exhibit more PPI than women, this ascertainment bias artificially diminishes control vs schizophrenia group differences. Menstrual cyclicity of PPI adds uncontrolled variance that may differentially affect control vs patient samples, and without carefully timed measurements, this “state-sensitive” cyclicity of PPI must diminish apparent heritability. Nevertheless, PPI deficits have been reported in both male and female schizophrenia patients.^{37,45,49}

Specific Genes Associated With PPI. Three lines of evidence implicate specific genes or gene regions in the regulation of PPI. First, PPI deficits in both HD^{23,58} and 22q11 deletion syndrome⁵⁹ suggest that the genes affected in both these disorders modify brain circuitry that regulates PPI. In both cases, animal models with homologous genetic defects also exhibit PPI deficits.^{25,60} Second, quantitative trait loci (QTLs) have been identified either through interval mapping in inbred rat strains (QTLs on chromosomes 2 and 18)⁶¹ or recombinant congenic mouse strains (5 QTLs across chromosomes 3, 5, 7, and 16)⁶² or through the use of chromosome substitution strains in mice (2 QTLs on chromosome 16).⁶³ Third, reverse genetic approaches have identified a long list of genes which, when inactivated via constitutive or conditional knock out techniques, are associated with a reduction in PPI.⁶⁴

Most genes associated with lower vs higher levels of PPI may be unrelated to reduced PPI in schizophrenia or other disease states. The most potent physiological influence on acoustic PPI is hearing threshold because an organism that cannot detect a prepulse will not exhibit PPI. Thus, many or most candidate “PPI genes” identified via gene inactivation or mapping strategies in inbred and recombinant rodents will likely be associated with hearing threshold. Beyond the level of sensory registration, the most potent physiological influence on PPI is exerted at the level of the pedunculopontine nucleus (PPTg), which mediates PPI via its impact on the NRPC.⁶⁵ For the same reasons noted for hearing threshold, genetic studies of PPI will likely be influenced strongly by genes coding for the normal function of the PPTg—a structure that does not play a central role in models of the pathophysiology of schizophrenia. In contrast, the PFC—which is suspected to be a critical substrate for some symptoms of schizophrenia—is likely to be 3 or 4 synapses removed from the primary startle circuit and, in a normal human or rodent, genes controlling the PFC will likely contribute only weakly to any gene mapping “signal” based on levels of PPI.

Conversely, we know that the HD gene exerts a powerful control on the viability of striatal circuitry that regulates PPI and that this gene is strongly associated with low or absent levels of PPI in humans and animal models. Yet, despite this, it is almost certain that no gene mapping efforts based on the PPI phenotype in normal rodent strains, or reverse genetic models based on constitutive or conditional knockout strategies (absent the insertion of the HD gene), will ever link the HD gene to low levels of PPI. Importantly, PPI is a measure that reflects the normal function of specific brain circuits, and genes associated with PPI deficits in neuropsychiatric disorders are likely to be ones that contribute uniquely to dysfunction in those brain circuits. Such genes will be most effectively identified through the use of affected and at-risk individuals, in whom deficient PPI is used as an endophe-

notype—a surrogate marker for neural circuit dysfunction that contributes to the vulnerability for the expression of the full clinical phenotype.

P50 Auditory Evoked Potential Suppression

The P50 wave is a midlatency auditory evoked potential that exhibits reduced amplitude, or suppression, when a second click sound is presented 500 ms after an initial click. This paired-click experimental procedure is referred to as the conditioning-testing paradigm.⁶⁶ Although the functional significance for this response suppression has not been clearly established, it is thought to reflect the brain’s inhibitory control of its response to stimuli.¹¹ In this model of response suppression, the first click stimulus initiates or conditions the inhibition and the second tests its strength. Thus, the conditioning response is generally maximal because no inhibitory circuits have yet been activated, and the test response is smaller because of the action of these inhibitory mechanisms. Alternative explanations of P50 suppression have been proposed, such as a protracted refractory or recovery period following the first click response. This explanation is contradicted, however, by the finding that the P50 test response actually increases when the interstimulus interval becomes very short (eg, 100 ms).⁶⁷ The generally accepted measure of the inhibitory gating effect is the ratio of the test amplitude to the conditioning amplitude.

Experimental Procedures. Subjects typically are supine, with their neck supported to minimize myogenic artifacts. The auditory stimuli are clicks, delivered 50 dB over the subject’s auditory threshold.⁶⁸ The stimuli are presented in trains of pairs, with an intrapair interval of 0.5 seconds and an interpair interval of 10 seconds. Subjects are instructed simply to remain awake, with their eyes open and fixed at a distant target; a behavioral response is not required. Electroencephalographic (EEG) activity is monitored, recorded and processed according to previously published methods.^{68–70} Trials containing EEG or electro-oculographic (EOG) activity greater than 30 μ V within the first 80 ms following the auditory stimulus are rejected. The operationalization of this criterion replaces an earlier procedure that relied on the technician’s judgment to accept or reject individual trials.

The conditioning P50 wave is identified as the most positive peak of the average auditory evoked potential, occurring 40–80 ms after the conditioning stimulus, measured relative to the preceding negative trough. To be accepted, a P50 wave must be $>0.5 \mu$ V, and any corresponding EOG activity must be lower in amplitude than the P50 wave itself. The test wave is identified as the most positive peak occurring after the test stimulus, within ± 10 ms of the latency of the conditioning response. The ratio of the P50 test and conditioning amplitudes defines the strength of the inhibitory response, with a larger value indicating less robust inhibition or suppression. Figure 2

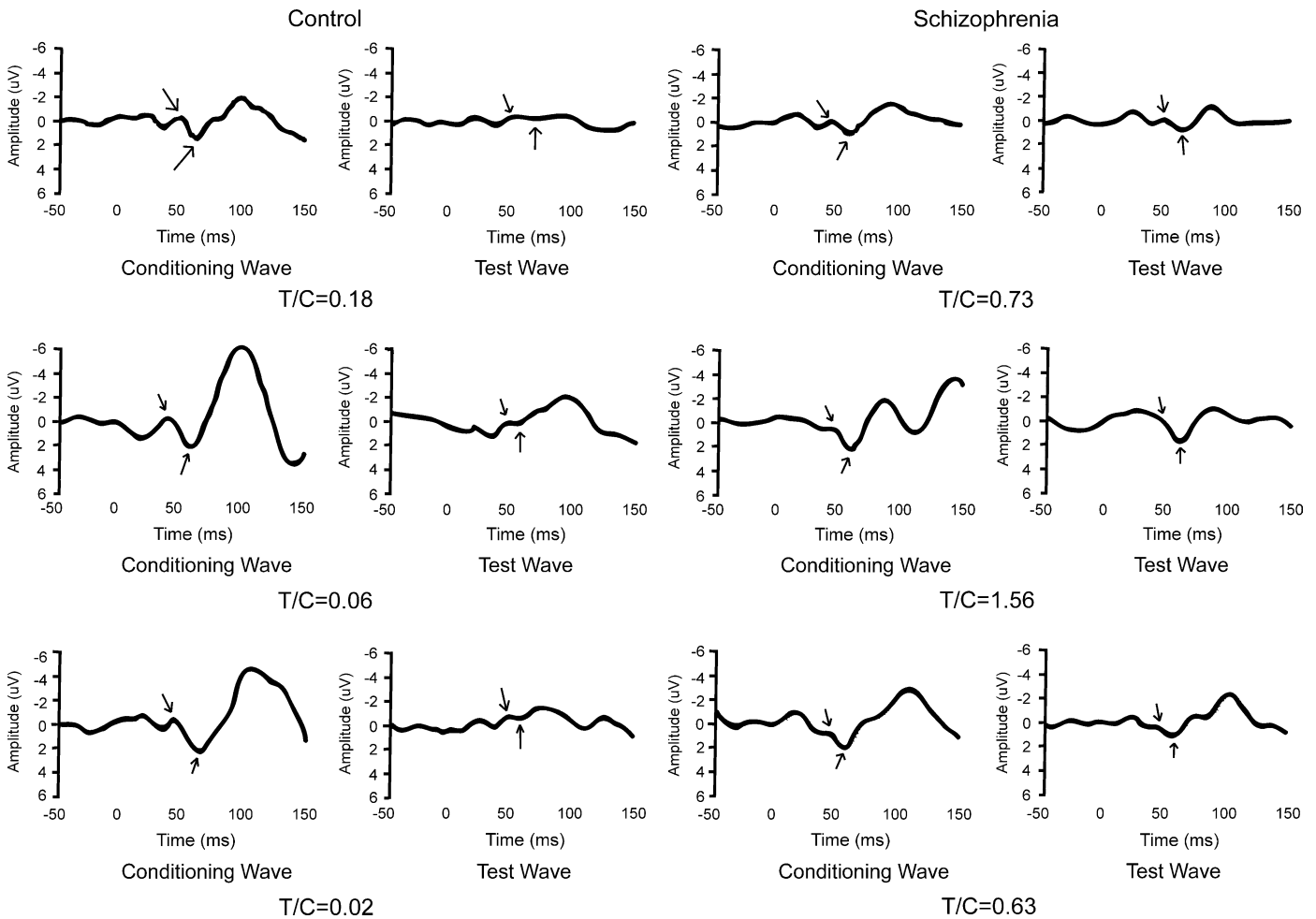


Fig. 2. Auditory evoked responses of 3 control subjects (left) and 3 subjects with schizophrenia (right). Stimuli were a conditioning auditory stimulus and an identical test stimulus delivered 500 ms apart. Arrows mark the location of the P50 wave in the tracings. Positive polarity is downward. Test-to-conditioning (T/C) ratio is indicated for each subject. P50 response to the second stimulus is attenuated in control subjects. As illustrated, schizophrenia patients typically exhibit less attenuation of the P50 response to this “test” click.

illustrates the test and conditioning responses in both schizophrenia patients and healthy control subjects.

The P50 is a relatively small ERP component, and questions have been raised concerning the effect of noise on the detection and measurement of the P50 signal. To address this question, a detailed trial-by-trial statistical analysis of P50 measurement has been performed.⁷¹ This analysis demonstrated that normal subjects had average evoked P50 conditioning responses that were significantly larger than the prestimulus EEG activity. Their test responses, in contrast, were not significantly different from the prestimulus EEG. Schizophrenia subjects had conditioning waves that were both similar in amplitude to those of controls and significantly different from the prestimulus activity. However, the patients’ test responses were also significantly larger than the prestimulus EEG. In the single-trial analysis, selection of the largest wave in the 40–80 ms poststimulus interval resulted in identical amplitudes for prestimulus, condi-

tioning and test periods in both normal and schizophrenia subjects. This demonstrates that, although the signal-to-noise ratio is too low to reliably identify the P50 wave in individual trials, averaging increases the signal-to-noise ratio to a level that is adequate to reliably distinguish the P50 response from background activity.

Neurobiology of P50 suppression. P50 suppression is regulated by wide-ranging neural circuitry, prominently involving hippocampal structures⁷² as evidenced from depth recordings in humans using an electrode that penetrated the hippocampus⁷³ and single-neuron recordings.⁷⁴ The penetrating recordings showed that the hippocampus generates a response 50 ms poststimulus, and the neuronal recordings showed that the response to repeated stimulation quickly diminishes. These findings in humans have been modeled in rats to determine the underlying synaptic mechanisms. Ablation of the CA3-CA4 area of the hippocampus, in rats, eliminates

the P20-N40 complex, considered the analog of the human P50.⁷⁵ One major input pathway to CA3-CA4 is from the medial septal nucleus through the fimbria-fornix. Lesion of this cholinergic pathway causes CA3 and CA4 neurons to lose their gating response to sensory stimuli. Cholinergic inputs to CA3-CA4 are further implicated by the fact that antagonists of the lower affinity nicotinic receptors, such as α -bungarotoxin, block the gating response⁷⁶; antagonists of high-affinity nicotinic receptors, such as mecamylamine, or muscarinic receptor antagonists have no effect on gating.

CA3-CA4 interneurons might be the final mechanism for suppression, as they are activated by this cholinergic input. These interneurons release γ -aminobutyric acid (GABA) onto the pyramidal neuron, which depresses its membrane potential so that it cannot discharge. GABA activates GABA_A- and GABA_B-type receptors on the pyramidal neuron, which together inhibit neuronal firing for up to 300 ms. A still longer inhibition may involve presynaptic GABA_B receptors located on the perforant pathways' synaptic terminals on the apical dendrites of the CA3 neurons. Although GABA is released primarily at the cell body of the CA3 neurons, if enough GABA is released by burst of interneuron activity, it may diffuse to the apical dendrites and contact GABA_B receptors on the presynaptic terminals of the perforant pathway fibers, inhibiting their release of the excitatory neurotransmitter glutamate. Then the perforant path can no longer send sensory information to the CA3 pyramidal neuron, so the response to the test stimulus is diminished. Activation of the interneurons' nicotinic receptors by cholinergic medial septal inputs could provide the additional burst activity for sufficient GABA release.

It is important to note that sensory gating has also been observed in other brain regions. Using a combination of hippocampal depth electrodes, subdural strip, and grid electrodes in epilepsy patients, evidence of sensory gating was found in the hippocampus, the temporoparietal region (Brodmann's area 22 and 2) and the PFC (Brodmann's areas 6 and 24), with the neocortical habituating responses peaking around 50 ms and hippocampal responses peaking around 250 ms poststimulus.⁷⁷ This suggests that sensory gating may be a multistep process with an early temporoparietal and prefrontal phase and a later hippocampal phase. The extent to which the gating deficits observed in schizophrenia are mediated by hippocampal vs other cortical or subcortical inputs remains a matter of some debate.

That brain cholinergic systems regulate at least some of these gating deficits is supported by findings that P50 suppression abnormalities in both schizophrenia patients⁵² and their relatives⁷⁸ resolve temporarily after administration of the cholinergic nicotinic receptor stimulant, nicotine. Further evidence for nicotinic involvement in schizophrenia is the decreased expression of

the α -7 nicotinic receptor as evidenced by ¹²⁴I- α -bungarotoxin binding or immunoreactivity.⁷⁹⁻⁸³ Noradrenergic neurotransmission may also be involved in the P50 auditory evoked response. Administration of yohimbine affects the release of norepinephrine by the blockade of alpha-2 presynaptic noradrenergic receptors that normally inhibit norepinephrine release. Yohimbine causes loss of auditory evoked potential gating in humans and rats.^{84,85} Although norepinephrine is probably not a major determinant of the abnormality in inhibition in schizophrenia, there is some correlation with plasma 3-Methoxy-4-Hydroxyphenylglycol levels.⁸⁶

Abnormality in Schizophrenia. Initial studies by Adler et al,⁸⁷ Freedman et al,^{88,89} and Siegel et al⁹⁰ showed that there was a failure of P50 suppression in schizophrenia patients, consistent with theories of failed inhibitory function.⁹¹ The deficit has been associated with diminished performance on neuropsychological measures of attention.⁹² Some groups have failed to replicate this finding, while others have replicated it but found it to be unrelated to self-reports of sensory disturbance.⁹³⁻⁹⁵ A common misconception, in this regard, is that normal inhibition means that healthy subjects do not hear the second sound. The role of inhibition is not to block all sound or other stimuli from reaching the hippocampus. Rather, it blocks weaker stimuli so that the responses to strong stimuli are emphasized. In the absence of inhibition, the hippocampus becomes hyperactive and then it can no longer respond to stimuli, a phenomenon called "occlusion." Evidence for occluded responses to novel stimuli in the hippocampus, in schizophrenia, comes from several types of neuroimaging studies.⁹⁶ The inhibition of weaker stimuli is also easily overcome by making the stimuli more relevant.⁹⁷

P50 suppression deficits in schizophrenia patients are persistent⁹⁸ and found in both acutely ill and more stable schizophrenic outpatients.^{87,88,99} The P50 deficit is present in both predominantly positive symptom and negative symptom patients,¹⁰⁰ though some studies have reported that the phenomenon is significant mainly in the disorganized/undifferentiated patients compared with the paranoid subtypes.¹⁰¹ P50 suppression deficits are also present in schizotypal patients.¹⁰²

Unmedicated schizophrenia patients have unusually small P50 waves, and the amplitude of the waves is normalized by neuroleptic treatment.¹⁰³ However, although the P50 increases in amplitude during treatment, it increases for both the conditioning and the test responses, so that the P50 ratio remains abnormally high. Individuals treated with clozapine, though, exhibit normalization of their P50 ratios coincident with improvement in their clinical symptoms.^{104,105} Clozapine, which releases acetylcholine in the hippocampus, may thereby indirectly act on the nicotinic receptor to normalize the P50 ratio, as people with schizophrenia also decrease

the number of cigarettes they smoke while taking this medication.¹⁰⁶ Clozapine also has the property of 5-Hydroxytryptamine 3 (5HT3) antagonism, which activates the nicotinic receptor. Acute administration of odansetron, a highly selective 5HT3 antagonist, induces a similar effect of improvement in P50 auditory gating in schizophrenia.¹⁰⁷ Direct α -7 nicotinic receptor agonism with 3-(2,4-dimethoxybenzylidene) anabaseine also normalizes the P50 ratio in a double-blind, placebo-controlled study of 12 people with schizophrenia.¹⁰⁸ Other atypical neuroleptics which may not have direct nicotinic agonism or 5HT3 antagonism have more variable effects on the P50 ratio. In 2 separate investigations,^{109,110} risperidone had only a marginal effect on P50 suppression, while olanzapine normalized it in one study¹¹⁰ and partially improved it in the other.¹⁰⁹ A third study¹¹¹ of 14 schizophrenia patients assigned to double-blind treatment with haloperidol or olanzapine found no group differences in P50 ratio. Thus, while risperidone does not appear to highly influence gating, the data on olanzapine remain inconsistent.

Reliability. Problems in test-retest reliability have been noted by several investigators.¹¹² Although conditioning and test amplitudes were reliably measured, the test-to-conditioning ratio was not. All cerebral evoked potential measurements include both a signal and a noise component. A ratio measurement that includes noise in both the numerator and the denominator will approach an asymptote of 1 as the noise increases.¹¹³ This problem is exacerbated by the relatively low signal-to-noise ratio of the P50 compared with other auditory evoked potential components. Though a reliable test-to-conditioning ratio is difficult to obtain due to its inherent mathematical properties, ie, test and conditioning are not independent, so that the shared variance between test and conditioning cannot be completely eliminated,^{112,113} the test-to-conditioning ratio nevertheless has the greatest power to distinguish normal subjects from schizophrenic subjects.¹¹³ Furthermore, the schizophrenia P50 suppression deficit has been reliably reproduced in large numbers of subjects across multiple sites.^{99,114-119}

Stability. Waldo *et al*¹²⁰ measured P50 suppression in 13 normal subjects, 10 days apart. P50 suppression was 66.5% on day 1 and 69.5% on day 10. There was no significant change in the gating of auditory test responses over this period. The change between days for individual subjects was generally within the 8% mean variability observed with repeated recordings in other groups of normal subjects. Griffith *et al*⁶⁸ recorded 10 schizophrenia patients and 10 healthy subjects on 3 occasions. The intraclass correlation was 0.73. Additionally, Hall *et al*¹²¹ measured P50 suppression in 19 MZ twin pairs on 2 separate occasions and found a P50 ratio intraclass correlation of 0.66.

Heritability. Young *et al*¹²² examined P50 suppression in 15 normal MZ twin pairs and 12 normal DZ twin pairs. The upper limit of the heritability estimate (calculated as twice the difference between the MZ and DZ intraclass correlations) was 1.0. The 95% confidence limit for the lower limit of heritability was 0.44. Hall *et al*¹²¹ examined P50 suppression in 40 healthy MZ twin pairs and 30 DZ twin pairs and reported a heritability estimate for the P50 test-to-conditioning ratio of 68%. Interestingly, preliminary heritability analysis of the COGS data sample ($n = 201$) revealed a nonsignificant heritability estimate of 0.07 for the test-to-conditioning ratio. However, the difference in amplitude between the P50 responses to the first and second clicks, which is an alternate way of measuring suppression, had quite high heritability ($h^2 = 0.53$, $P = .005$) (T. A. Greenwood, D. L. Braff, K. S. Cadenhead, M. E. Calkins, D. J. Dobie, R. Freedman, M. F. Green, R. E. Gur, G. A. Light, J. Mintz, K. H. Nuechterlein, A. Olincy, A. D. Radant, L. J. Seidman, L. J. Siever, J. M. Silverman, W. S. Stone, N. R. Swerdlow, D. W. Tsuang, M. T. Tsuang, B. I. Turetsky, N. J. Schork unpublished data).

Specific Genes Associated with P50 Suppression. The P50 auditory evoked potential endophenotype has been linked with a genetic marker at the locus of the *CHRNA7*, the gene coding for the α -7 subunit of the nicotinic receptor.¹²³ Furthermore, the presence of a single nucleotide polymorphism in the 15q14 gene *CHRNA7* 5' core promoter is significantly associated with P50 suppression deficits ($P = .008$).¹¹⁰ Association of *CHRNA7* polymorphisms with P50 gating has been replicated, but the specific allelic associations differ, which suggests that responsible mutations have not yet been unambiguously identified.¹²⁴⁻¹²⁶

AS Eye Movement Dysfunction

The AS task, first described in 1978¹²⁷ utilizes the intrinsically precise and quantifiable nature of oculomotor performance to assess a specific aspect of oculomotor/cognitive function.

Experimental Procedures. To perform the AS task, subjects are seated in a dark room with their heads stabilized, and their eye position is ascertained with high precision, typically using infrared oculography or EOG, while they watch a specialized sequence of dot movements. A single AS trial commences with fixation on a central point, followed by an unpredictably located stimulus to the left or right. Rather than looking at this stimulus, the subject is asked to look at the mirror image location on the opposite side of the screen. Thus, the participant must inhibit an unwanted, reflexive saccade to the stimulus. A cue then appears signaling the location of a correct response and then the target returns to central fixation for the next trial.

Duration of each task component, the number of potential different AS target locations, and maximal and minimum distances from center, vary across studies. There may be a gap, simultaneous offset and onset, or overlap between central fixation and the AS cue stimulus, and this factor appears to affect the magnitude of schizophrenia-control differences.¹²⁸ Direction of the first major saccade determines whether the subject has made an incorrect AS (sometimes referred to as a “prosaccade” or reflexive error) vs a correct AS. Figure 3 illustrates the infrared tracings associated with correct and incorrect AS performance. The summary variable is typically the proportion of incorrect (error) saccades, or sometimes proportion of correct AS, over all trials.

Neurobiology of AS. Correct performance of the AS task requires accurate perception, ability to transform location information to a mirror image representation, and suppression of a reflexive visually guided saccade to the

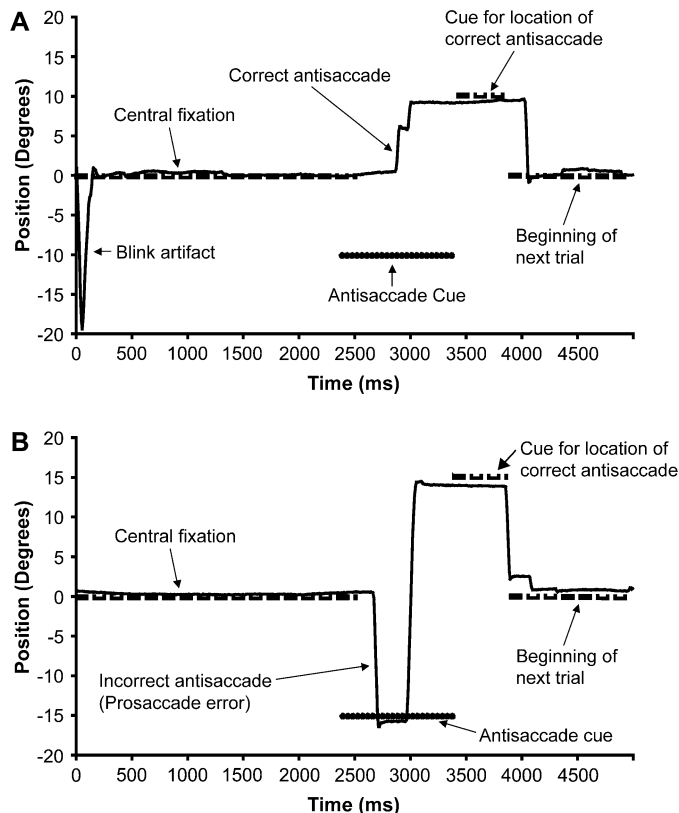


Fig. 3. Infrared tracings of eye position during 2 trials of a prototypical AS task. The participant is asked to generate a saccade in the opposite direction of the AS cue. In the first trial (A), the participant generates a correct AS, looking away from the cue. In the second trial (B), the participant initially makes an incorrect response (prosaccade error) to the AS cue and then quickly generates a large corrective saccade to the appropriate location. Position of the AS cue varies unpredictably from trial to trial. This particular version of the task has a 200-ms overlap between central fixation and the AS cue. Schizophrenia patients typically make more of these prosaccade errors than healthy subjects.

AS stimulus as well as nonspecific task demands such as motivation, ability to comprehend the task, and willingness to hold one’s head still.

While the oculomotor system is composed of many cortical and subcortical areas, certain areas appear crucial for accomplishing the unique demands of the AS task. Sensory transformation of location information appears to occur in the lateral interparietal area,^{129,130} although PFC may also be involved.¹³¹ Damage to dorso-lateral PFC causes decreased frequency of correct AS¹³² and specific neurons in PFC activate specifically during AS.^{133–136} Amemori et al¹³⁷ have argued that this phenomena reflects working memory. Finally, single-unit recordings in monkeys demonstrate that supplementary eye field neurons are active during tasks that require generation of saccades based on internal representations of location including the AS task.¹³⁸ Thus, parietal, prefrontal, and supplementary oculomotor areas appear uniquely relevant to AS performance.

Neuroimaging and performance data indicate that basic sensorimotor processes involved in visually guided saccade generation appear essentially normal in schizophrenia.¹³⁹ Because schizophrenia patients generally make at least 50% of correct AS responses, and often will generate corrective saccades despite an initially incorrect response, they clearly understand the task itself and appear to have sufficient motivation. Raemaekers et al,¹⁴⁰ using functional magnetic resonance imaging (fMRI) found that while schizophrenia patients activated frontal and parietal areas normally during an AS task, they failed to activate the striatum as much as controls and concluded that dysfunction of a frontal striatal saccade suppression network explains the poor performance of schizophrenia patients. Patients with lesions of dorso-lateral PFC and/or abnormalities of the caudate exhibit increased AS error rates, while patients with cortical lesions of the frontal eye fields, supplementary eye fields, posterior parietal cortex, and temporal cortex do not.¹⁴¹ This suggests that the increased error rate observed in schizophrenia patients, described below, is consistent with dorsolateral prefrontal cortical dysfunction.^{142,143} Imaging^{144,145} and ERP¹⁴⁶ studies in schizophrenia patients and healthy individuals have tended to support this conclusion, though not ubiquitously.¹⁴⁷

Abnormality in Schizophrenia. In the late 1980’s, Fukushima et al¹⁴⁸ reported that schizophrenia patients evince a greater number of inappropriate reflexive saccades to the target in an AS task than nonpsychiatric controls. Since then, more than 50 studies have consistently reported this effect.^{149–159} Notably, there have been no investigations, to our knowledge, failing to find that schizophrenia patients generate more errors than controls. Moreover, particular AS task manipulations have been reported to enhance the magnitude of effect.^{128,160–163}

Inconsistencies in the literature have been noted regarding the diagnostic specificity of this AS dysfunction to schizophrenia patients,^{143,164} with some reports of increased AS error rates in members of other psychiatric disorders, such as major depression¹⁶⁵ and bipolar disorder.¹⁶⁶ Conversely, evidence has been cited suggesting that increased AS error rates do not characterize performance of mood or anxiety disordered patients.¹⁶⁷ Although the question is unresolved, increased error rates in mood disorder patients would not be deleterious to the endophenotype status of AS performance; eye movement dysfunction in some mood disorder patients may reflect shared genetic susceptibility influencing mechanisms that contribute to both clinical state and poor AS performance.¹⁶⁸

While error rate has been most extensively investigated in schizophrenia, other parameters, including latency, gain, and accuracy, have also been examined. Anomalies in response latency may provide evidence of visual processing inefficiencies. Schizophrenia patients have been reported to exhibit longer latencies on correct AS responses than control subjects,^{128,160,169} potentially reflecting compensatory slowing due to difficulties inhibiting unwanted reflexive saccades.¹⁶⁰ Although less commonly measured, latencies to error responses suggest that they do not differentiate schizophrenia patients from nonpsychiatric controls.^{160,161} Latency to correct responses thus appears to tap an aspect of performance that is distinct from latency to incorrect responses, highlighting the importance of differentiating the 2, a distinction that is not routinely made in current investigations.

Several studies have reported reduced spatial accuracy of AS in schizophrenia patients.^{128,150,158,169,170} This abnormality may implicate parietal and prefrontal cortical control of sensorimotor coordinate transformations¹⁵⁰ or impairment in generating saccades from internal representations in the supplementary motor area.

Reliability. A number of studies have shown good test-retest reliability of AS error rate over periods ranging from several months to many years among patients with schizotypy,¹⁷¹ schizophrenia patients,^{172,173} first-degree relatives,¹⁷³ and controls.¹⁷⁴ Our recent analysis of data from the COGS sample of schizophrenia patients ($n = 103$) and community comparison subjects ($n = 138$) suggests high within-session reliability of the AS paradigm at 7 sites (range = 0.77–0.96).¹⁷⁵ Moreover, there were no significant cross-site differences in performance, suggesting that high-quality AS data can be obtained across multiple sites using standardized measures, equipment, and training procedures.¹⁷⁵

Stability. Recent studies of the test-retest stability of AS error rates have suggested high temporal stability in schizophrenia patients ($r = .87$, test-retest interval = 2.78 years),¹⁷² and in a mixed group of schizophrenia

patients and their relatives ($r = .73$, test-retest interval = 1.82 years).¹⁷³ The results are consistent with 2 other reports examining performance in groups of psychiatric patients ($r = .75$, test-retest interval = 1 year,¹⁷⁶ $r = .90$, test-retest interval = 1 week¹⁷⁷). It has been reported that first-episode,^{158,178–180} remitted,¹⁴² and unmedicated¹⁸¹ schizophrenia patients all manifest AS deficits, further suggesting that the deficits are not merely a reflection of clinical state or chronicity of illness. The majority of studies examining the relationship between medication and AS error rates have described the results as non-significant.^{140,148,161,180,182–187} However, there is some evidence that AS performance in schizophrenia may actually improve with nicotine administration^{155,188} and with some medications, including risperidone¹⁸⁹ and cyproheptadine treatment.¹⁹⁰ Nonetheless, in general, the AS deficit observed in schizophrenia is temporally stable and does not appear to be attributable to clinical variables such as medication exposure, current symptomatology, and chronic illness. Thus, the available evidence is consistent with the trait stability of the AS deficit in schizophrenia patients.

Heritability. Malone and Iacono,¹⁹¹ using a large sample of identical and fraternal healthy twin girls, found a high heritability of 0.57 for AS performance; no other published studies have examined heritability. However, preliminary analysis of the COGS data ($n = 340$) found a very similar heritability estimate of 0.49 ($P < .0001$) (T. A. Greenwood, D. L. Braff, K. S. Cadenhead, M. E. Calkins, D. J. Dobie, R. Freedman, M. F. Green, R. E. Gur, G. A. Light, J. Mintz, K. H. Nuechterlein, A. Olincy, A. D. Radant, L. J. Seidman, L. J. Siever, J. M. Silverman, W. S. Stone, N. R. Swerdlow, D. W. Tsuang, M. T. Tsuang, B. I. Turetsky, N. J. Schork unpublished data). Numerous studies have investigated the familiarity of poor performance in schizophrenia by evaluating performance of first-degree biological relatives of schizophrenia patients. The presence of increased AS error rates in relatives has been described as inconsistently demonstrated.^{151,192,193} Two recent meta-analyses quantitatively evaluated the magnitude of the relative-control difference. Levy *et al.*¹⁹³ reviewed selected studies ($k = 9$) using the “standard” (nonoverlap and nongap) version of the AS task and obtained a moderate mean magnitude of effect between relatives and controls (mean Cohen $d = 0.43$). Calkins *et al.*¹⁵⁹ included 17 independent groups of relatives and all AS studies regardless of AS paradigm. Meta-analysis yielded an increased AS error rate in relatives vs controls at a moderate to large magnitude of effect (mean Cohen $d = 0.61$). The results of both meta-analyses suggest that, on average, relatives of schizophrenia patients produce a greater number of AS errors than controls.

In their review, Levy *et al.*¹⁹³ conducted moderator analyses and concluded that schizophrenia relatives appear impaired in the AS task because studies use more

stringent inclusion criteria for controls than relatives, in effect leading to the spurious appearance of a deficit in relatives. However, because there are so few studies in this realm, Calkins et al¹⁵⁹ conducted a reanalysis of primary data¹⁴² in which they varied inclusion and exclusion criteria and found impairment even in medically and psychiatrically healthy relatives who were screened comparably to controls. More recently, Ettinger et al¹⁵⁰ compared psychiatrically healthy controls with comparably screened siblings of schizophrenia patients and obtained an effect size of 0.49. Thus, the impairment observed in relatives does not appear attributable to inclusionary criteria practices, at least in these 2 investigations. Instead, the differences across studies may lie not in the controls or their selection criteria, but in the relatives, perhaps vis-à-vis proband or relative inclusion criteria.¹⁵⁹ Nonetheless, this methodological issue underscores the importance of carefully addressing and analyzing the potential impact of comorbid psychiatric and medical conditions on AS performance in both relatives and comparison subjects.

A small number of studies suggest that, like schizophrenia patients, relatives tend to demonstrate longer latencies to correct trials.¹⁶¹ Two studies examining spatial accuracy of AS in relatives reported reduced AS gain in healthy siblings¹⁵⁰ and in unaffected MZ cotwins of patients with schizophrenia,¹⁴⁹ compared with healthy controls. These results are suggestive that, in addition to error rates, AS gain and latency are worthy of further investigation as candidate endophenotypes.

Specific Genes Associated With AS Performance. The only genetic study to include the AS task reported linkage at *D22S315* on chromosome 22q11–12 in 8 schizophrenia multiplex families when relatives were identified by either an AS deficit or a P50 sensory gating deficit.¹⁹⁴ The composite endophenotype identified substantially more relatives as affected than did either of the endophenotypes alone, likely enhancing the power to detect linkage. While the linkage finding has yet to be replicated, the results are particularly notable because the linked region is the site of the catechol-O-methyltransferase (COMT) gene, variations of which have been linked to performance on candidate endophenotypes believed to reflect PFC abilities in schizophrenia patients and their relatives.¹⁹⁵ Given the apparent involvement of the dorsolateral prefrontal cortex in the accurate performance of the AS task, the association between AS performance (and/or P50) and chromosome 22q could be partially explicable by COMT effects. However, given the small size and lack of replication, this result must be regarded as preliminary.

Measures of Impaired Deviance Detection

MMN

MMN is an auditory ERP component that is elicited when a sequence of repetitive standard sounds is inter-

rupted infrequently by deviant, “oddball” stimuli (eg, infrequent stimuli that differ in duration or pitch from the more frequently presented stimuli). The MMN occurs rapidly: following deviant stimuli, the response onset can be as early as 50 ms and peaks after an additional 100–150 ms. Physiologically, MMN is the first measurable brain response component that differentiates between frequent and deviant auditory stimuli and reflects the properties of an automatic, memory-based comparison process.¹⁹⁶

MMN has many advantages for psychiatric and cognitive neuroscience studies, including the exploration of the neural substrates of schizophrenia and its treatment.^{197–199} First, MMN can be rapidly assessed and is highly stable in normal subjects.^{200–202} In a longitudinal study of schizophrenia patients retested after 1 year, Light and Braff²⁰³ found extremely high MMN reliability coefficients (intra-class correlations ~0.90). Second, the mismatch response appears to reflect a predominantly automatic process: it is not under subject control, requires no overt behavioral response from subjects, and can be elicited while subjects perform other mental activities in parallel without apparent interaction or interference.²⁰⁴ In this context, well-defined MMN waveforms can be obtained from sleeping infants,^{205–207} adults,^{208,209} patients with extremely severe brain injuries, and even comatose patients.^{210–212} Because MMN occurs even in the absence of conscious and effortful attention, it appears to index a preattentive form of sensorimemory.²⁰⁴ While later ERP components occurring 300–500 ms after stimulus presentation (eg, P3b) are also sensitive to changes in stimulus characteristics and sequencing, they are only elicited in response to attended stimuli and are therefore associated with attention-dependent and active cognitive processes. Attention-dependent cognitive functions assessed by traditional neuropsychological tests or long-latency ERP methods (eg, P3b) can be markedly influenced by motivational factors, level of task engagement, performance incentives, self-monitoring, and emotional factors.^{213–218} In contrast, preattentive cognitive measures such as MMN offer promise for accurately characterizing the integrity of sensory network dysfunction free of attentional or motivational artifacts in studies of neuropsychiatric patient populations.^{199,219}

Experimental Procedures. In the prototypical MMN paradigm, an unchanging standard tone is presented repeatedly with a brief interstimulus interval (eg, 500 ms). The relatively rapid stimulus presentation ensures that the echoic memory trace of the preceding stimulus is still active when the subsequent stimulus is presented. The repeating standard tone is replaced infrequently (eg, 10% of trials) by a deviant tone that differs in one physical attribute. This is typically a change in either the pitch or the duration of the tone, though stimulus intensity has also been used to define deviance. Subjects are not instructed

to attend to or respond to the tones in any way. In most cases, attention is specifically directed away from the tones through the use of a visual distracter, such as a video, or an active visual attention task. This ensures that the automatic detection of deviance at the level of echoic memory is not obscured by responses related to controlled or directed attention. Figure 4 illustrates the auditory ERP responses to the standard and pitch deviant stimuli, in patients and healthy control subjects. Measurement of MMN is carried out on the difference waveform constructed by subtracting the auditory evoked potential response to the standard tone from that of the deviant. MMN appears as a prominent negative potential on this difference waveform. For a pitch deviant, its peak latency is typically between 100 and 200 ms poststimulus, but this is more variable for a duration deviant. The am-

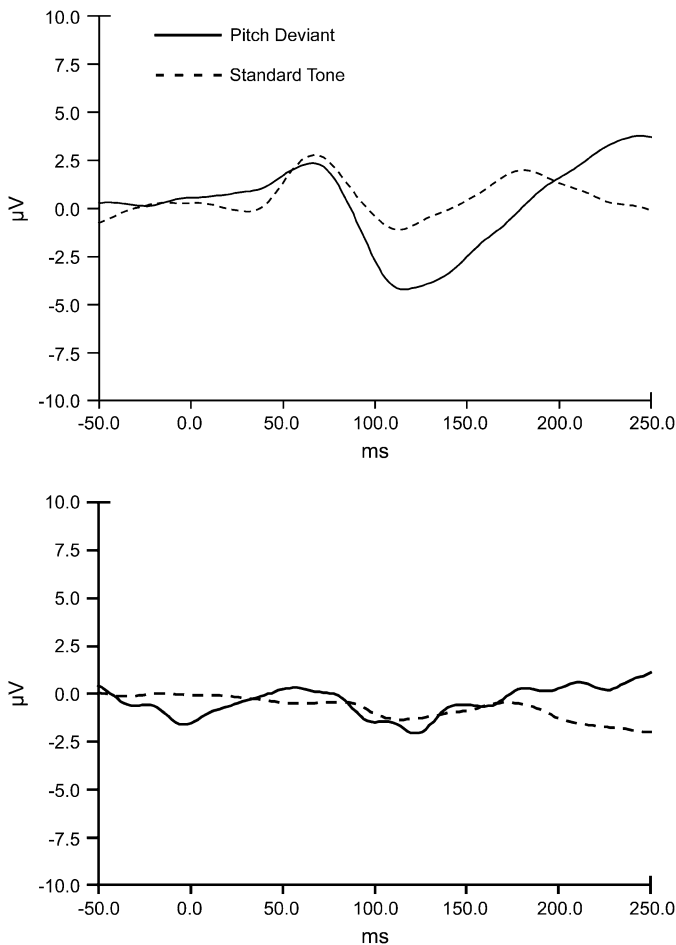


Fig. 4. MMN response to an auditory pitch-deviant stimulus. The MMN elicited by a 2000-Hz deviant tone is seen as a negative deflection between 100 and 150 ms poststimulus, with maximum deflection at Fz. The repeating standard, in this case, was a 1000-Hz tone presented every 500 ms, and the deviant tone comprised 5% of the stimuli. Top: grand average waveforms for 20 control subjects. Bottom: grand average waveforms for 19 patients. As shown, schizophrenia patients typically exhibit smaller MMN amplitudes than healthy subjects.

plitude of MMN is a function of the magnitude of the physical difference between the standard and deviant stimuli.

Neurobiology of MMN. In the auditory domain, maximal mismatch responses are evident at frontocentral scalp recording sites with phase reversal at posterior scalp electrodes (eg, mastoids).²⁰⁴ Magnetoencephalography, high-density EEG, functional imaging, and studies of patients with discrete brain lesions indicate that the auditory MMN is generated within the primary and secondary auditory cortices with possible contributions from bilateral dorsolateral prefrontal cortices.^{220–230} In addition, MMN is often utilized to probe frontotemporal brain systems across a range of developmental and neuropsychiatric disorders.^{199,211,231–235}

Previous studies have demonstrated that NMDA may play a crucial role in both the generation of MMN and the MMN deficits observed in schizophrenia (see below). NMDA receptor antagonists selectively diminish MMN generation in awake monkeys,²³⁶ and subanesthetic doses of ketamine, an NMDA antagonist, selectively decrease MMN in healthy human volunteers without affecting other ERP activity.²³⁷ Umbricht et al²³⁸ also found that lower baseline MMN was significantly associated with psychotic-like behavioral effects and experiences induced by subsequent ketamine administration. Thus, MMN may serve as a neurophysiological “assay” of NMDA receptor functioning in models of schizophrenia.

Abnormality in Schizophrenia. Deficits in MMN represent a remarkably robust finding in schizophrenia research. Shelley et al²³⁹ first identified MMN deficits in schizophrenia patients using deviant stimuli that differed in duration (ie, duration MMN) from standard stimuli. Since that time, there have been several published reports of reduced MMN in schizophrenia patients utilizing various stimulation parameters (eg, pitch, duration, and intensity stimulus manipulations) and conditions.^{198,240} In a recent meta-analysis performed by Umbricht and Krljes,²⁴⁰ the mean effect size for the schizophrenia deficit was ~ 1.0 —a large deficit according to common standards. Also, though it was not a statistically significant difference, the effect size was approximately 40% larger for studies that used a duration deviant, compared with studies that used a frequency deviant. While the meaning of this remains unclear, it likely implicates task-specific neural mechanisms that underlie the schizophrenia deficit and is therefore a very intriguing, if still only suggestive, difference. Importantly, in contrast to most other physiological indices, MMN deficits appear to be relatively specific to schizophrenia. Bipolar, major depressive^{241,242} and obsessive-compulsive disorder patients^{243–245} all have normal MMNs, though there are reports of MMN deficits among chronic alcoholics.²⁴⁶

Reliability. There is substantial evidence to indicate that MMN has good test-retest reliability.²⁰² In a study of 15 healthy individuals tested on 2 separate occasions 1–27 days apart, Tervaniemi et al²⁴⁷ examined the reliability of MMN for deviant stimuli that varied in duration, pitch, or intensity. Reliability was greatest for the duration deviant ($r = .78$) and lowest for the pitch deviant ($r = .53$). Kathmann et al²⁰⁰ reported very similar estimates from a study of 45 subjects tested 2–4 weeks apart. Test-retest reliability, in this case, was >0.8 for a duration deviant and ~ 0.5 for a pitch deviant. Escera et al²⁴⁸ observed reliabilities of 0.72 and 0.80 for a duration-deviant MMN, depending upon whether the peak or the mean within a defined time interval was used to measure MMN amplitude. Kujala et al²⁰¹ noted test-retest correlations of 0.60–0.75, depending on the degree of deviance of the infrequent stimulus. Only one small study ($n = 14$)²⁴⁹ reported correlation coefficients that were described as unacceptable. Most importantly, the one study reporting the results of repeat testing in schizophrenia patients²⁰³ found intraclass correlations of ~ 0.90 after 1 year.

Stability. In schizophrenia patients, MMN deficits do not appear to be ameliorated by first-generation antipsychotic medications,²⁵⁰ risperidone,²⁵¹ olanzapine,²⁵² or clozapine.^{229,250} Similarly, clinical changes from acute to post-acute phases of illness do not correspond to a “normalization” of MMN deficits in chronic patients.²⁵³ In chronic schizophrenia patients, MMN deficits are highly associated with impairments in real-world functioning and level of independence in community living situation.^{203,254,255}

Heritability. There are no studies that have attempted to formally estimate the heritability of MMN. We know of no studies that have examined MZ vs DZ twin-pair correlations or considered the differences between intrafamilial and interfamilial associations. However, there are reports of specific genetic associations (see below), which indicate a degree of genetic modulation of MMN. Also, animal models of the MMN indicate NMDA-mediated differences in auditory deviance processing among genetically distinct inbred mouse strains.²⁵⁶ It is reasonable to expect, therefore, that the normal heritability of MMN will ultimately prove to be comparable to that of the other physiological measures considered here.

Whether or not this is true for the heritability of the schizophrenia abnormality, though, is not clear. Clinically unaffected family members of schizophrenia patients,^{257,258} children at risk for developing schizophrenia,^{259,260} and recent-onset patients^{261,262} have all been reported to have reduced MMN amplitudes. MMN would appear, therefore, to be a specific schizophrenia-related endophenotype^{8,258} for studying the complex genetics of the disorder.^{12,13} However, there have also been

reports of normal MMNs in unaffected family members.²⁶³ Moreover, in contrast to the virtually universal finding of abnormal MMNs among chronic schizophrenia patients, MMNs have been reported to be normal in first-episode patients.^{262,264} Longitudinal follow-up suggests that the MMN deficit may emerge over time in concert with the progressive temporal lobe volume loss that occurs over the early course of the illness (D. F. Salisbury, personal communication). The degree of MMN impairment may also be modulated by the level of premorbid educational achievement in first-episode patients.²⁶² Additional studies are therefore needed to clearly delineate the nature of the MMN abnormality, its prevalence among putatively prodromal or first-episode schizophrenia subjects, and its utility for predicting conversion to psychosis in individuals at genetically high risk for developing the disorder.²⁶⁵

Specific Genes Associated With MMN. Deletions of chromosome 22q result in complex congenital syndromes that frequently include schizophrenia-like psychoses. Two studies of adolescents with 22q deletions have now demonstrated that this is associated with diminished MMN.^{266,267} The 22q deletion includes the COMT gene, which codes for the enzyme that deactivates DA, leading to regionally specific hyperdopaminergia. Reduced MMN was associated with the presence of the MET allele of the VAL108/158MET polymorphism of the COMT gene in the remaining copy on the unaffected chromosome.²⁶⁷ This suggests that genetic modulation of dopaminergic activity can affect MMN, a finding that is of obvious relevance to schizophrenia. Importantly, the limited evidence of association between COMT and schizophrenia suggests that the VAL, rather than the MET, allele may confer an increased risk of disease.^{195,268} However, it is difficult to make specific inferences concerning the physiological effects of the VAL/MET polymorphism in schizophrenia because this is contingent upon both the background level of dopaminergic activity and the presence or absence of other modifying genes.²⁶⁹ The only other genetic association study reported no relationship between ApoE allelic variation and MMN among older individuals with mild cognitive impairment.²⁷⁰

P300

The P300 event-related brain potential is an index of endogenous cognitive processes, typically elicited by infrequent sensory stimuli that are either task relevant or novel.²⁷¹ It receives its name from its appearance as a large vertex-positive component with peak latency approximately 300 ms after stimulus presentation. Occurring after the obligate evoked potential response to the physical attributes of a stimulus, it reflects a variety of cognitive processes elicited by a change in the sensory environment. These include directed attention, the contextual updating

of working memory, and the attribution of salience to a deviant stimulus. Since its discovery in 1965, it has been widely investigated, with a multitude of studies examining the clinical and psychological correlates of P300 amplitude and latency, in both healthy and clinical populations.²⁷²

Experimental Procedures. Although it can be elicited by stimuli in any sensory modality, it is the auditory P300 that has been most widely studied in schizophrenia patients. The prototypical experimental paradigm has been the oddball task in which an infrequent tone, designated as the “target,” is randomly interspersed within an ongoing train of a different repeating tone, designated as the standard. Subjects are instructed to indicate their perception of each target by making a button press or other response. The task is designed to be quite simple, with a relatively slow stimulus presentation rate (1- to 2-second interstimulus interval) and a large pitch difference (eg, 1000 Hz standard and 2000 Hz target). Schizophrenia patients typically achieve >90% correct target identifications. Figure 5 illustrates the auditory ERP responses to target and standard tones, in patients and healthy control subjects. A variant of the oddball task, known as the “3-tone” or “novelty” P300 paradigm, adds an additional infrequent stimulus which is not the designated target; instead, it is distinctive, variable, and somewhat intrusive in its physical attributes but is intended to be ignored by the subject.

Neurobiology of P300. It is now clearly established that the P300 is not a unitary phenomenon. Rather, it is a composite representation of the activity of temporally overlapping but anatomically and functionally distinct neural generators. Experimental task manipulations have elucidated at least 2 functionally discrete subcomponents. The P3a subcomponent, which is elicited by stimuli that are novel or unexpected (as in the 3-tone or novelty paradigm), occurs slightly earlier, has a frontocentral topographic scalp distribution and appears to reflect attentional orienting processes.²⁷³ P3b, in contrast, is elicited by stimuli that are task relevant and contextually salient (as in the oddball paradigm). It occurs later, has a parietal scalp maximum, and reflects cognitive processes associated with stimulus evaluation and response formation. Intracranial electrophysiological monitoring and fMRI studies have similarly discerned multiple sources of P300-like ERP activity, including the hippocampus,^{274–277} thalamus,^{277,278} inferior parietal lobe,^{275,277} superior temporal gyrus, and frontal lobe.^{275,277,279} It is unlikely, though, that deeper sources such as the hippocampus or thalamus contribute substantially to the P300 as measured on the scalp. Convergent evidence from ERP source localization and fMRI activation studies, as well as recordings from patients with focal neurological lesions, suggests that P3b scalp activity arises primarily from the inferior parietal cortex, particularly the supramarginal gyrus, while the P3a reflects the activ-

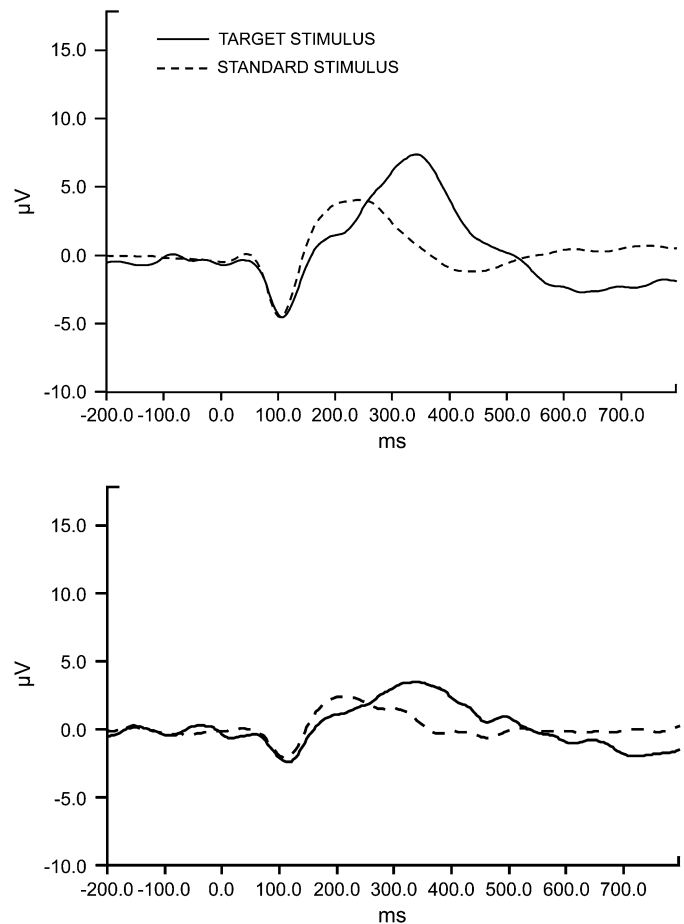


Fig. 5. P300 response to an infrequent salient auditory stimulus. The P300 response to a target stimulus appears as a broad positive ERP component between 300 and 400 ms poststimulus, with maximum amplitude at the Pz electrode. In this example, subjects made a button press to a 2000-Hz target tone. The standard tone was 1000 Hz. Tones were presented every 1.8 seconds. Top: grand average waveforms for 38 control subjects. Bottom: grand average waveforms for 52 patients. As shown, schizophrenia patients typically exhibit smaller P300 amplitudes than healthy subjects.

ity of lateral prefrontal and superior temporal areas.²⁸⁰ However, specific neural circuits or neurotransmitters underlying the P300 response are not clearly defined.

Abnormality in Schizophrenia. Reduced amplitude of the auditory oddball P300 response is perhaps the most robust physiological abnormality observed in schizophrenia patients, having been replicated repeatedly with virtually uniform consistency.^{272,281–283} While prolonged P300 latency has also been reported,²⁸⁴ this appears to be a much more equivocal and less reliable finding. This may be due, in part, to differences in patient populations across studies. A recent meta-analysis of 104 studies reported a significant effect size of 0.59 for auditory P300 latency (compared with an effect size of 0.89 for amplitude).²⁸⁵ However, this analysis also reported that the latency effect size diminished with illness duration,

making it a less reliable finding among studies of chronic patients. Investigations have now begun to move beyond the simple documentation of a cohort deficit to elucidate the clinical, familial, and neuroanatomical correlates of the amplitude decrement. There is now considerable evidence that this represents a trait abnormality that is independent of medication status, duration of illness, or symptom severity.^{286–289} Although state-dependent relationships have been reported between P300 amplitude and measures of negative symptomatology,²⁹⁰ positive symptomatology,²⁹¹ treatment status,²⁹² and stage of illness,²⁹³ it is clear from both longitudinal and meta-analytic studies that P300 amplitude does not normalize in patients, even when treated with newer atypical antipsychotic agents.^{285,286,289,292–296} Consistent with this idea of a trait abnormality, McCarley and associates have reported that the greatest P300 amplitude separation between schizophrenics and normals is observed at left temporal electrode sites^{291,297} and that this focal decrement is correlated with a decreased left superior temporal gyrus volume.²⁹⁸ Although these studies have focused primarily on the P3b subcomponent, there is some evidence to indicate that P3a is also reduced in schizophrenia patients^{299,300} and that this deficit is associated with decreased gray matter volume in the frontal lobe.³⁰¹

It is important to note that, despite the highly reproducible and persistent nature of the schizophrenia P300 abnormality, the deficit is not specific to this disorder. Consistent with its multifactorial role in information processing and its distributed neural substrate, the P300 response is disrupted in a variety of neuropsychiatric disorders that included disturbed cognition. Reduced P300 amplitude has been observed in, among others, Alzheimer's disease,³⁰² alcoholism,³⁰³ bipolar illness,³⁰⁴ and unipolar depression.³⁰⁵ It is notable, though, that in Alzheimer's disease the decreased amplitude is also associated with marked latency prolongation, in bipolar illness it is associated with a different scalp topography, in depression it is a state-dependent abnormality evident only during acute depressive episodes, and in alcoholism it is more abnormal in the visual than the auditory domain. These variations suggest that different neural mechanisms may underlie the deficit in different disorders.

Reliability. Despite its multidimensional character, scalp measurements of P300 amplitude exhibit very good test-retest reliability.^{296,306–311} Studies of healthy control subjects with test-retest intervals of up to 2 weeks have documented reliabilities ranging from 0.81 to 0.91.^{296,306,307} One study of 32 subjects retested after 4.5 months reported test-retest correlations of 0.79–0.81.³⁰⁹ Two studies with even longer intertest intervals (14 and 24 months) had test-retest reliabilities of 0.59 and 0.61, respectively.^{310,311} In a study of both schizophrenia patients and controls tested twice over the course

of 1–3 years, Turetsky et al²⁸⁹ reported reliabilities of 0.86 for controls and 0.61 for patients.

Stability. As noted above, many studies have reported persistent longitudinal deficits in schizophrenia, despite active treatment and marked symptom reduction. Comparisons across sites, however, are hampered by a lack of uniformity in both the experimental protocol parameters and the methods used to measure P300 amplitude. Different laboratories focus on different electrode sites. Some measure peak amplitude at a single time point, while others use the area under the curve within a specified time interval. Still others use sophisticated decomposition strategies to estimate individual subcomponent amplitudes. As a common metric, we examined the patient/control amplitude ratio at Pz. For a large sample from our laboratory at the University of Pennsylvania, this value was 0.64. Comparable values extracted from 5 published studies were 0.59,³¹² 0.61,³⁰⁴ 0.69,³¹³ 0.77,²⁹⁴ and 0.80.³¹⁴ This indicates highly consistent findings across independent laboratories.

Heritability. There is strong evidence of a genetic contribution to P300 amplitude among healthy individuals. The most convincing data are from a study by O'Connor et al.³¹⁵ In a sample of 59 MZ and 39 same-sex DZ twin pairs, heritability was estimated to be 0.60. Consistent with this, Polich and Burns³¹⁶ reported a correlation of 0.64 between MZ twin pairs, compared with -0.20 for unrelated matched pairs. A recent large-scale study of adolescent twin pairs reported that additive genetic factors accounted for 48%–61% of the variance in P3 amplitude.³¹⁷ A second similar study found that familial factors accounted for 30%–81% of the variance among adolescent twin pairs. In this case, the familial covariance could be attributed primarily to genetic factors among the males but to shared environmental factors among the females.³¹⁸ In another study of 10 healthy families, each consisting of 2 parents and 2 children, Eischen and Polich³¹⁹ reported Fisher z -transformed correlation coefficients of $\sim +0.40$ for within-family associations, but ~ -0.02 associations between unrelated individuals. Only one smaller study³²⁰ failed to find evidence of heritability; MZ and DZ sib-pairs had intrapair correlations, respectively, of 0.50 and 0.35, but this was a nonsignificant difference.

There is also substantial evidence that the schizophrenia trait abnormality is, at least in part, genetically mediated.^{260,321–325} Studies of individuals who share a portion of the genetic diathesis for schizophrenia, by virtue of being either the full siblings or offspring of schizophrenia patient probands, have P300 amplitude decrements that are similar to, though less severe than, those of their ill relatives.^{260,287,321–324,326} Frangou et al,³²² in the Maudsley family study, reported standardized z scores of -1.03 in 57 family members compared with healthy controls. In a study notable for its methodology

of examining MZ twin pairs both concordant and discordant for schizophrenia, Weisbrod *et al.*³²⁷ observed decreased amplitudes in both affected and unaffected cotwins of the patient probands, compared with healthy twin pairs. Only a handful of studies have considered topographic differences that reflect the relative contributions of P3a and P3b subcomponents to this familial deficit. Kimble *et al.*³²⁵ observed z score measurements of -0.48 at Pz and -0.68 at Fz in 15 first-degree relatives. They argued that the greater frontal deficit reflected heritable impairments specifically in the attentional processes underlying P300. Another study that deconstructed the scalp P300 into its discrete P3a and P3b subcomponents³²⁶ also found that the familial deficit was evident for the frontal P3a subcomponent ($z = -0.71$) but not for the parietal P3b. These 2 findings are consistent with behavioral findings from high-risk family studies, which also suggest that abnormalities in attention are indicators of biological susceptibility.³²⁸ A more recent study, however, reported that both schizophrenia patients and their unaffected siblings had increased frontal P300 amplitudes, along with the expected decrease in the parietal P300 response.³²⁹ So, although the evidence for a P300 abnormality in the unaffected first-degree relatives of patients is quite strong, the relative contributions of P3a and P3b remain unclear.

Specific Genes Associated With P300. Although evidence supporting the viability of P300 as a physiological endophenotype is strong, there is only limited knowledge of specific genetic contributions to either the generation or the disruption of the ERP response. Most of what is known is derived from the Collaborative Study on the Genetics of Alcoholism studies of the visual P300 in the context of alcohol risk and may not, therefore, be applicable to schizophrenia. Nevertheless, these studies demonstrated relatively strong linkages (LOD Score > 2.3) between P300 amplitude decrements and areas of chromosomes 2, 5, 6, and 17.^{330,331} Of these, only the region of chromosome 6, which contains the dysbindin candidate gene, has also been implicated in schizophrenia.³³² A specific association has also been reported, among children at risk for alcoholism, between reduced auditory P300 amplitude and the A1 allele of the *DRD2* DA receptor on chromosome 11.³³³ The relationship between genetic determinants of dopaminergic function and P300 is further supported by the association between P300 amplitude and the Ser9Gly polymorphism of the *DRD3* DA receptor in healthy subjects.³³⁴ These findings are not specifically linked to either schizophrenia or the schizophrenia P300 deficit. Nevertheless, the obvious importance of DA to both the symptomatology and treatment of schizophrenia makes them intriguing.

The only evidence of a specific genetic association to reduced P300 amplitude in schizophrenia comes from the study of a large family pedigree with a balanced trans-

location of the long arm of chromosome 1 and the short arm of chromosome 11.³³⁵ This translocation disrupts the *DISC1* gene at the chromosome 1 breakpoint and is strongly linked to schizophrenia (LOD Score = 3.6). Among the members of this family, those with the translocation exhibited reduced P300 amplitudes compared with both familial noncarriers and unrelated control subjects. This association was observed even among carriers of the translocation who exhibited no psychiatric symptoms, strongly implicating P300 amplitude as an endophenotypic marker of the *DISC1* genetic vulnerability.

Conclusion

The ideal neurophysiological endophenotype is one that exhibits a robust and stable deficit in both patients and unaffected family members and shows strong evidence of both heritability and cosegregation with illness within pedigrees. It also should be easily and rapidly measured with minimal subject demands, demonstrate excellent test-retest and across-site reliability, and, preferably, reflect a discrete neurobiological mechanism that is both informative for the pathophysiology of the disorder and regulated by a limited number of genes. Each of these 5 candidate endophenotypes has been shown to be abnormal in schizophrenia patients. For 4 of the 5, there is also strong evidence that the abnormality is heritable and present in unaffected family members of schizophrenia probands. The one exception to this is MMN, which is not unequivocally impaired in either newly diagnosed patients or unaffected first-degree relatives. It should be noted, though, that there is very little evidence that any of these measures actually cosegregate with the illness within individual pedigrees. This is a reflection of the lack of such comprehensive family studies, rather than an indication of negative findings.

Of the 4 remaining measures, 2—PPI and P50—have the distinct advantage of being preattentive indices of relatively discrete neural mechanisms that can be assessed without any observable patient response. They, therefore, require much less motivation, cooperation, or comprehension from the subject. However, they are both influenced by state-dependent factors that add additional nongenetic noise to their measurement. The most notable of these is their tendency toward normalization by atypical antipsychotic medications, which could confound a quantitative trait linkage analysis. The 2 remaining candidate endophenotypes—AS and P300—both appear to be highly stable trait measures that are reliably assessed and impervious to the effects of treatment. However, these require a level of subject cooperation that presents a challenge for assessment in the most severely ill patients. Also, these are more complex behavioral tasks that rely upon a more distributed neural network and, therefore, a presumably more complex genetic architecture. It is ironic that, of all these measures, MMN

perhaps best fulfills the combined criteria of simplicity, reliability, and state independence. It is therefore extremely important that the status of this deficit in unaffected family members, high-risk individuals, and newly diagnosed patients be clarified using a standardized methodology.

As indicated in the introduction to this review, there is growing interest in the concept of multivariate endophenotypes. A composite endophenotype comprised of multiple measures may exhibit greater experimental stability and test-retest reliability than a single endophenotype. It may thus be a more robust marker of genetic vulnerability than any one measure. Also, to the extent that one measure can act as a surrogate for another, then the relative merits of each might allow them to be selectively applied under different circumstances. For example, one measure of inhibitory failure (eg, PPI) might be assessed in an unmotivated patient taking a typical antipsychotic, while another (eg, AS) might be measured in a cooperative patient taking an atypical agent. However, the extent to which these putative endophenotypes overlap with each other and denote the same genetic vulnerability is an issue that remains relatively unaddressed. Only rarely have multiple measures been acquired in the same patient samples. One study that assessed 4 of these endophenotypes (PPI omitted) in schizophrenia patients, relatives, and controls replicated the deficits but found no meaningful correlations across measures, with the one exception of a robust association between P50 and AS.⁸ Another comparably structured study, though, failed to find any association between these 2 indices.¹⁵³ There are data demonstrating a similar lack of association, in schizophrenia, between PPI and AS,¹⁵² as well as both animal³³⁶ and human^{337,338} data suggesting a dissociation between PPI and P50. It is telling that a recent study of P50, MMN, and P300 in healthy MZ and DZ twins⁹ found, once again, that each of these 3 measures was highly heritable but that they shared virtually no genetic contributions.

The strong implication of these aggregation studies is that, although these measures may share a common conceptual framework (ie, inhibitory failure or impaired deviance detection), they probably reflect different neurobiological and genetic substrates. Although no one measure is an ideal physiological endophenotype neither is any one of them redundant. Rather, each is likely to denote an independent contribution to the overall genetic vulnerability to schizophrenia. In this case, individuals who are impaired on more than one measure are more likely to be those who have the highest genetic loading for the illness and to be most informative for genetic linkage and association studies.⁹ Conversely, individuals who are impaired on different measures may reflect different variants of genetic risk that could assist in the identification of distinct genetic subtypes of schizophrenia. Future studies should therefore focus on the assessment of multiple endophenotypic measures in the same individuals and families, despite the methodological difficulties

that this would entail. Detailed investigations of the interrelatedness of these measures will enable us to better address questions regarding both the possible heterogeneity and underlying etiologic mechanisms of the disorder. Large-scale multisite investigations, such as the National Institute of Mental Health-funded COGS, described elsewhere in this Issue,³³⁹ will be in an ideal position to perform such analyses.

References

1. Gottesman II, Gould TD. The endophenotype concept in psychiatry: etymology and strategic intentions. *Am J Psychiatry*. 2003;160:636–645.
2. Iacono WG. Identifying psychophysiological risk for psychopathology: examples from substance abuse and schizophrenia research. *Psychophysiology*. 1998;35:621–637.
3. Gould TD, Gottesman II. Psychiatric endophenotypes and the development of valid animal models. *Genes Brain Behav*. 2006;5:113–119.
4. Almasy L, Blangero J. Endophenotypes as quantitative risk factors for psychiatric disease: rationale and study design. *Am J Med Genet*. 2001;105:42–44.
5. Grove WM, Lebow BS, Clementz BA, Cerri A, Medus C, Iacono WG. Familial prevalence and coaggregation of schizotypy indicators: a multitrait family study. *J Abnorm Psychol*. 1991;100:115–121.
6. Iacono WG, Clementz BA. A strategy for elucidating genetic influences on complex psychopathological syndromes (with special reference to ocular motor functioning and schizophrenia). *Prog Exp Pers Psychopathol Res*. 1993;16:11–65.
7. Calkins ME, Iacono WG. Eye movement dysfunction in schizophrenia: a heritable characteristic for enhancing phenotype definition. *Am J Med Genet*. 2000;97:72–76.
8. Price GW, Michie PT, Johnston J, et al. A multivariate electrophysiological endophenotype, from a unitary cohort, shows greater research utility than any single feature in the Western Australian Family Study of Schizophrenia. *Biol Psychiatry*. 2006;60:1–10.
9. Hall MH, Schulze K, Bramon E, Murray RM, Sham P, Rijdsdijk F. Genetic overlap between P300, P50, and duration mismatch negativity. *Am J Med Genet B Neuropsychiatr Genet*. 2006;141B:336–343.
10. Iacono WG, Carlson SR, Malone SM. Identifying a multivariate endophenotype for substance use disorders using psychophysiological measures. *Int J Psychophysiol*. 2000;38:81–96.
11. Venables P. Input dysfunction in schizophrenia. In: Maher BA, ed. *Progress in Experimental Personality Research*. Orlando, Fla: Academic Press; 1964:1–47.
12. Braff DL, Freedman R. Endophenotypes in studies of the genetics of schizophrenia. In: Davis KL, Charney DS, Coyle JT, Nemeroff C, eds. *Neuropsychopharmacology: The Fifth Generation of Progress*. Philadelphia, Pa: Lippincott Williams & Wilkins; 2002:703–716.
13. Braff DL, Light GA. The use of neurophysiological endophenotypes to understand the genetic basis of schizophrenia. *Dialogues Clin Neurosci*. 2005;7:125–135.
14. Graham F. The more or less startling effects of weak prestimuli. *Psychophysiology*. 1975;12:238–248.
15. Braff D, Stone C, Callaway E, Geyer M, Glick I, Bali L. Prestimulus effects on human startle reflex in normals and schizophrenics. *Psychophysiology*. 1978;15:339–343.

16. Cadenhead KS, Swerdlow NR, Shafer KM, Diaz M, Braff DL. Modulation of the startle response and startle laterality in relatives of schizophrenia patients and schizotypal personality disordered subjects: evidence of inhibitory deficits. *Am J Psychiatry*. 2000;157:1660–1668.
17. Cadenhead KS, Swerdlow NR, Braff DL. Relative risk of prepulse inhibition deficits in schizophrenia patients and their siblings. *Biol Psychiatry*. 2001;49:126S.
18. Kumari V, Das M, Zachariah E, Ettinger U, Sharma T. Reduced prepulse inhibition in unaffected siblings of schizophrenia patients. *Psychophysiology*. 2005;42:588–594.
19. Braff DL, Geyer MA, Swerdlow NR. Human studies of prepulse inhibition of startle: normal subjects, patient groups, and pharmacological studies. *Psychopharmacology*. 2001;156:234–258.
20. Braff DL, Grillon C, Geyer M. Gating and habituation of the startle reflex in schizophrenic patients. *Arch Gen Psychiatry*. 1992;49:206–215.
21. Swerdlow NR, Geyer MA, Braff DL. Neural circuitry of prepulse inhibition of startle in the rat: current knowledge and future challenges. *Psychopharmacology*. 2001;156:194–215.
22. Swerdlow NR, Paulsen J, Braff DL, Butters N, Geyer MA, Swenson MR. Impaired prepulse inhibition of acoustic and tactile startle in patients with Huntington's Disease. *J Neurol Neurosurg Psychiatry*. 1995;58:192–200.
23. Valls-Sole J, Munoz JE, Valdeoriola F. Abnormalities of prepulse inhibition do not depend on blink reflex excitability: a study in Parkinson's disease and Huntington's disease. *Clin Neurophysiol*. 2004;115:1527–1536.
24. Kodsí MH, Swerdlow NR. Prepulse inhibition in the rat is regulated by ventral and caudodorsal striato-pallidal circuitry. *Behav Neurosci*. 1995;109:912–928.
25. Carter RJ, Lione LA, Humby T, et al. Characterization of progressive motor deficits in mice transgenic for the human Huntington's disease mutation. *J Neurosci*. 1999;19:3248–3257.
26. Kumari V, Gray JA, Geyer MA, et al. Neural correlates of tactile prepulse inhibition: a functional MRI study in normal and schizophrenic subjects. *Psychiatry Res*. 2003;122:99–113.
27. Geyer MA, Krebs-Thomson K, Braff DL, Swerdlow NR. Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. *Psychopharmacology*. 2001;156:117–154.
28. Karper LP, Freeman GK, Grillon C, Morgan CA III, Charney DS, Krystal JH. Preliminary evidence of an association between sensorimotor gating and distractibility in psychosis. *J Neuropsychiatry Clin Neurosci*. 1996;8:60–66.
29. Perry W, Braff DL. Information-processing deficits and thought disorder in schizophrenia. *Am J Psychiatry*. 1994;151:363–367.
30. Perry W, Geyer MA, Braff DL. Sensorimotor gating and thought disturbance measured in close temporal proximity in schizophrenic patients. *Arch Gen Psychiatry*. 1999;56:277–281.
31. Swerdlow NR, Light GA, Cadenhead KC, Sprock J, Hsieh MH, Braff DL. Startle gating deficits in a large cohort of patients with schizophrenia: relationship to medications, symptoms, neurocognition and level of function. *Arch Gen Psychiatry*. In press.
32. Abel K, Waikar M, Pedro B, Hemsley D, Geyer M. Repeated testing of prepulse inhibition and habituation of the startle reflex: a study in healthy human controls. *J Psychopharmacol*. 1998;12:330–337.
33. Flaten MA. Test-retest reliability of the somatosensory blink reflex and its inhibition. *Int J Psychophysiology*. 2002;45:261–265.
34. Cadenhead KS, Carasso BS, Swerdlow NR, Geyer MA, Braff DL. Prepulse inhibition and habituation of the startle response are stable neurobiological measures in a normal male population. *Biol Psychiatry*. 1999;45:360–364.
35. Swerdlow NR, Talledo JA. Baseline startle gating predicts post-placebo gating 1–2 weeks later [abstract]. *Biol Psychiatry*. 2005;57:40S–41S.
36. Braff DL, Swerdlow NR, Geyer MA. Symptom correlates of prepulse inhibition deficits in male schizophrenic patients. *Am J Psychiatry*. 1999;156:596–602.
37. Braff DL, Light GA, Ellwanger J, Sprock J, Swerdlow NR. Female schizophrenia patients have prepulse inhibition deficits. *Biol Psychiatry*. 2005;57:817–820.
38. Leumann L, Feldon J, Vollenweider FX, Ludewig K. Effects of typical and atypical antipsychotics on prepulse inhibition and latent inhibition in chronic schizophrenia. *Biol Psychiatry*. 2002;52:729–739.
39. Ludewig K, Geyer MA, Etzensberger M, Vollenweider FX. Stability of the acoustic startle reflex, prepulse inhibition, and habituation in schizophrenia. *Schizophr Res*. 2002;55:129–137.
40. Weike AI, Bauer U, Hamm AO. Effective neuroleptic medication removes prepulse inhibition deficits in schizophrenia patients. *Biol Psychiatry*. 2000;47:61–70.
41. Meincke U, Morth D, Voss T, Thelen B, Geyer MA, Gouzoulis-Mayfrank E. Prepulse inhibition of the acoustically evoked startle reflex in patients with an acute schizophrenic psychosis—a longitudinal study. *Eur Arch Psychiatry Clin Neurosci*. 2004;254:415–421.
42. Francis DD, Szegda K, Campbell G, Martin WD, Insel TR. Epigenetic sources of behavioral differences in mice. *Nat Neurosci*. 2003;6:445–446.
43. Willott JF, Tanner L, O'Steen J, Johnson KR, Bogue MA, Gagnon L. Acoustic startle and prepulse inhibition in 40 inbred strains of mice. *Behav Neurosci*. 2003;117:716–727.
44. Anokhin AP, Heath AC, Myers E, Ralano A, Wood S. Genetic influences on prepulse inhibition of startle reflex in humans. *Neurosci Lett*. 2003;353:45–48.
45. Jovanovic T, Szilagyí S, Chakravorty S, et al. Menstrual cycle phase effects on prepulse inhibition of acoustic startle. *Psychophysiology*. 2004;41:401–406.
46. Swerdlow NR, Hartman PL, Auerbach PP. Changes in sensorimotor inhibition across the menstrual cycle: implications for neuropsychiatric disorders. *Biol Psychiatry*. 1997;41:452–460.
47. Kumari V, Soni W, Sharma T. Normalization of information processing deficits in schizophrenia with clozapine. *Am J Psychiatry*. 1999;156:1046–1051.
48. Swerdlow NR, Talledo J, Sutherland AN, Nagy D, Shoemaker JM. Antipsychotic effects on prepulse inhibition in normal 'low gating' humans and rats. *Neuropsychopharmacology*. 2006;31:2011–2021.
49. Braff DL, Geyer MA, Light GA, et al. Impact of prepulse characteristics on the detection of sensorimotor gating deficits in schizophrenia. *Schizophr Res*. 2001;49:171–178.
50. Mackeprang T, Kristiansen KT, Glenthøj BY. Effects of antipsychotics on prepulse inhibition of the startle response in drug-naïve schizophrenic patients. *Biol Psychiatry*. 2002;52:863–873.

51. Cadenhead KS, Geyer MA, Braff DL. Impaired startle prepulse inhibition and habituation in schizotypal patients. *Am J Psychiatry*. 1993;150:1862–1867.
52. Adler LE, Hoffer LD, Wiser A, Freedman R. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. *Am J Psychiatry*. 1993;150:1856–1861.
53. Duncan E, Madonick S, Chakravorty S, et al. Effects of smoking on acoustic startle and prepulse inhibition in humans. *Psychopharmacology*. 2001;156:266–272.
54. Kumari V, Soni W, Sharma T. Influence of cigarette smoking on prepulse inhibition of the acoustic startle response in schizophrenia. *Hum Psychopharmacol*. 2001;16:321–326.
55. Kumari V, Aasen I, Sharma T. Sex differences in prepulse inhibition deficits in chronic schizophrenia. *Schizophr Res*. 2004;69:219–235.
56. Rahman Q, Kumari V, Wilson GD. Sexual orientation-related differences in prepulse inhibition of the human startle response. *Behav Neurosci*. 2003;117:1096–1102.
57. Swerdlow NR, Monroe SM, Hartston HJ, Braff DL, Geyer MA, Auerbach PP. Men are more inhibited than women by weak prepulses. *Biol Psychiatry*. 1993;34:253–261.
58. Swerdlow NR, Filion D, Geyer MA, Braff DL. Normal personality correlates of sensorimotor, cognitive and visuo-spatial gating. *Biol Psychiatry*. 1995;37:286–299.
59. Sobin C, Kiley-Brabeck K, Karayiorgou M. Lower prepulse inhibition in children with the 22q11 deletion syndrome. *Am J Psychiatry*. 2005;162:1090–1099.
60. Paylor R, Glaser B, Mupo A, et al. Tbx1 haploinsufficiency is linked to behavioral disorders in mice and humans: implications for 22q11 deletion syndrome. *Proc Natl Acad Sci U S A*. 2006;103:7729–7734.
61. Palmer AA, Breen LL, Flodman P, Conti LH, Spence MA, Printz MP. Identification of quantitative trait loci for prepulse inhibition in rats. *Psychopharmacology*. 2003;165:270–279.
62. Joobar R, Zarate JM, Rouleau GA, Skamene E, Boksa P. Provisional mapping of quantitative trait loci modulating the acoustic startle response and prepulse inhibition of acoustic startle. *Neuropsychopharmacology*. 2002;27:765–781.
63. Petryshen TL, Kirby A, Hammer RP Jr, et al. Two quantitative trait loci for prepulse inhibition of startle identified on mouse chromosome 16 using chromosome substitution strains. *Genetics*. 2005;171:1895–1904.
64. Geyer MA, McIlwain KL, Paylor R. Mouse genetic models for prepulse inhibition: an early review. *Mol Psychiatry*. 2002;7:1039–1053.
65. Swerdlow NR, Geyer MA. Prepulse inhibition of acoustic startle in rats after lesions of the pedunculopontine tegmental nucleus. *Behav Neurosci*. 1993;107:104–117.
66. Eccles JC. *The Inhibitory Pathways of the Central Nervous System*. Liverpool, England: University Press; 1969.
67. Boutros NN, Belger A. Midlatency evoked potentials attenuation and augmentation reflect different aspects of sensory gating. *Biol Psychiatry*. 1999;45:9717–9722.
68. 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. *Psychophysiology*. 1995;32:460–466.
69. Griffith JM, Waldo M, Adler LE, Freedman R. Normalization of auditory sensory gating in schizophrenic patients after a brief period for sleep. *Psychiatry Res*. 1993;49:29–39.
70. Nagamoto HT, Adler LE, Waldo MC, Griffith J, Freedman R. Gating of auditory response in schizophrenics and normal controls. Effects of recording site and stimulation interval on the P50 wave. *Schizophr Res*. 1991;4:31–40.
71. Freedman R, Adler LE, Waldo M, et al. Inhibitory gating of an evoked response to repeated auditory stimuli in schizophrenic and normal subjects: human recordings, computer simulation, and an animal model. *Arch Gen Psychiatry*. 1996;53:1114–1121.
72. Waldo MC, Cawthra E, Adler LE, et al. Auditory sensory gating, hippocampal volume, and catecholamine metabolism in schizophrenics and their siblings. *Schizophr Res*. 1994;12:93–106.
73. Goff WR, Williamson PD, VanGilder JC, Allison T, Fisher TC. Neural origins of long latency evoked potentials recorded from the depth and from the cortical surface of the brain in man. *Prog Clin Neurophysiol*. 1980;7:126–145.
74. Wilson CL, Babb TL, Halgren E, Wang ML, Crandall PH. Habituation of human limbic neuronal response to sensory stimulation. *Exp Neurol*. 1984;7:126–145.
75. Nagamoto HT, Stevens KE, Fuller LL, Bernal S, Johnson R, Rose GM. Effects of intraventricular kainic acid on sensory gating of the rat N40 evoked potential [abstract]. *Soc Neurosci Abst*. 1990;16:1351.
76. Luntz-Leybman V, Bickford P, Freedman R. Cholinergic gating of response to auditory stimuli in rat hippocampus. *Brain Res*. 1992;587:130–136.
77. Grunwald T, Butros NN, Pezer N, et al. Neuronal substrates of sensory gating with the human brain. *Biol Psychiatry*. 2003;53:511–519.
78. Adler LE, Hoffer LJ, Griffith J, Waldo MC, Freedman R. Normalization by nicotine of deficient auditory sensory gating in the relatives of schizophrenics. *Biol Psychiatry*. 1992;32:607–616.
79. Freedman R, Hall M, Adler LE, Leonard S. Evidence in postmortem brain tissue for decreased numbers of hippocampal nicotinic receptors in schizophrenia. *Biol Psychiatry*. 1995;38:22–33.
80. Guan ZZ, Zhang X, Blennow K, Nordberg A. Decreased protein level of nicotinic receptor alpha7 subunit in the frontal cortex from schizophrenic brain. *Neuroreport*. 1999;10:1779–1782.
81. Martin-Ruiz CM, Haroutunian VH, Long P, et al. Dementia rating and nicotinic receptor expression in the prefrontal cortex in schizophrenia. *Biol Psychiatry*. 2003;54:1222–1233.
82. Court J, Spurden D, Lloyd S, et al. Neuronal nicotinic receptors in dementia with Lewy bodies and schizophrenia: alpha-bungarotoxin and nicotine binding in the thalamus. *J Neurochem*. 1999;73:1590–1597.
83. Marutle A, Zhang X, Court J, et al. Laminar distribution of nicotinic receptor subtypes in cortical regions in schizophrenia. *J Chem Neuroanat*. 2001;22:115–126.
84. Stevens KE, Meltzer J, Stryker SL, Rose GM. Disruption of sensory gating by the alpha-2 selective noradrenergic antagonist yohimbine. *Biol Psychiatry*. 1993;33:130–132.
85. Adler LE, Hoffer LD, Nagamoto HT, Waldo MC, Kiskey MA, Griffith JM. Yohimbine impairs P50 auditory sensory gating in normal subjects. *Neuropsychopharmacology*. 1994;10:249–257.
86. Kang D-Y, Poole J, McCallin K, Fein G, Vinogradov S. Sensory gating deficit in schizophrenia: relation to catecholamine metabolites. *Schizophr Res*. 1997;24:234.
87. Adler LE, Pachtman E, Franks RD, Pecevich M, Waldo MC, Freedman R. Neurophysiological evidence for a deficit

- in neuronal mechanisms involved in sensory gating in schizophrenia. *Biol Psychiatry*. 1982;17:639–654.
88. Freedman R, Adler LE, Waldo MC, Pachtman E, Franks RD. Neurophysiological evidence for a defect in inhibitory pathways in schizophrenia: comparison of medicated and drug-free patients. *Biol Psychiatry*. 1983;18:537–551.
 89. Freedman R, Adler LE, Gerhardt GA, et al. Neurobiological studies of sensory gating in schizophrenia. *Schizophr Bull*. 1987;13:669–678.
 90. Siegel C, Waldo M, Mizner G, Adler LE, Freedman R. Deficits in sensory gating in schizophrenic patients and their relatives. Evidence obtained with auditory evoked responses. *Arch Gen Psychiatry*. 1984;41:607–612.
 91. Braff DL, Geyer MA. Sensorimotor gating and schizophrenia: human and animal model studies. *Arch Gen Psychiatry*. 1990;47:181–188.
 92. Cullum CM, Harris JG, Waldo MC, et al. Neurophysiological and neuropsychological evidence for attentional dysfunction in schizophrenia. *Schizophr Res*. 1993;10:131–111.
 93. Kathmann N, Engel RR. Sensory gating in normals and schizophrenics: a failure to find strong P50 suppression in normals. *Biol Psychiatry*. 1990;27:1216–1226.
 94. Jin Y, Potkin SG, Patterson JV, Sandman CA, Hetrick WP, Bunney WE Jr. Effects of P50 temporal variability on sensory gating in schizophrenia. *Psychiatry Res*. 1997;70:71–81.
 95. Jin Y, Bunney WE Jr, Sandman CA, et al. Is P50 suppression a measure of sensory gating in schizophrenia? *Biol Psychiatry*. 1998;43:873–878.
 96. Heckers S. Neuroimaging studies of the hippocampus in schizophrenia. *Hippocampus*. 2001;11:520–528.
 97. Guterman Y, Josiasen RC, Bashore TR Jr. Attentional influence on the P50 component of the auditory event-related brain potential. *Int J Psychophysiol*. 1992;12:197–209.
 98. Franks RD, Adler LE, Waldo MC, Alpert J, Freedman R. Neurophysiological studies of sensory gating in mania: comparison with schizophrenia. *Biol Psychiatry*. 1983;18:989–1005.
 99. Ward PB, Hoffer LD, Liebert BJ, Catts SV, O'Donnell M, Adler LE. Replication of a P50 auditory gating deficit in Australian patients with schizophrenia. *Psychiatry Res*. 1996;64:121–135.
 100. Adler LE, Waldo M, Tacher A, Cawthra E, Baker N. Lack of relationship of auditory sensory gating defects to negative symptoms in schizophrenia. *Schizophr Res*. 1990;3:131–138.
 101. Boutros NN, Zouridakis G, Overall J. Replication and extension of P50 findings in schizophrenia. *Clin Electroencephalogr*. 1991;22:40–45.
 102. Cadenhead KS, Light GA, Geyer MA, Braff DL. Sensory gating deficits assessed by the P50 event-related potential in subjects with schizotypal personality disorder. *Am J Psychiatry*. 2000;157:55–59.
 103. Miller C, Freedman R. Medial septal neuron activity in relation to an auditory sensory gating paradigm. *Neuroscience*. 1993;55:373–380.
 104. Nagamoto HT, Adler LE, Hea RA, Griffith JM, McRae KA, Freedman R. Gating of auditory P50 in schizophrenics: unique effects of clozapine. *Biol Psychiatry*. 1996;40:181–188.
 105. Becker J, Gomes I, Ghisolfi ES, et al. Clozapine, but not typical antipsychotics, correct P50 suppression deficit in patients with schizophrenia. *Clin Neurophysiol*. 2004;115:396–401.
 106. McEvoy JP, Freudenreich O, Wilson WH. Smoking and therapeutic response to clozapine in patients with schizophrenia. *Biol Psychiatry*. 1999;46:125–129.
 107. Adler LE, Cawthra EM, Donovan KA, et al. Improved P50 auditory gating with ondansetron in medicated schizophrenia patients. *Am J Psychiatry*. 2005;162:386–388.
 108. Olincy A, Harris JG, Johnson LL, et al. Proof-of-concept trial of an $\alpha 7$ nicotinic agonist in schizophrenia. *Arch Gen Psychiatry*. 2006;63:630–638.
 109. Light GA, Geyer MA, Clementz BA, Cadenhead KS, Braff DL. Normal P50 suppression in schizophrenia patients treated with atypical antipsychotic medications. *Am J Psychiatry*. 2000;157:767–771.
 110. Adler LE, Olincy A, Cawthra EM, et al. Varied effects of atypical neuroleptics on P50 auditory gating in schizophrenia patients. *Am J Psychiatry*. 2004;161:1822–1828.
 111. Arango C, Summerfelt A, Buchanan RW. Olanzapine effects on auditory sensory gating in schizophrenia. *Am J Psychiatry*. 2003;160:2066–2068.
 112. Smith DA, Boutros NN, Schwarzkopf SB. Reliability of P50 auditory event-related potential indices of sensory gating. *Psychophysiology*. 1994;31:607–612.
 113. Adler LE, Freedman R, Ross RG, Olincy A, Waldo MC. Elementary phenotypes in the neurobiological and genetic study of schizophrenia. *Biol Psychiatry*. 1999;46:8–18.
 114. Clements BA, Geyer MA, Braff DL. Poor P50 suppression among schizophrenia patients and their first-degree biological relatives. *Am J Psychiatry*. 1998;155:1691–1694.
 115. Waldo MC, Gerhardt G, Baker N, Drebing C, Adler L, Freedman R. Auditory sensory gating and catecholamine metabolism in schizophrenic and normal subjects. *Psychiatry Res*. 1992;44:21–32.
 116. Freedman R, Coon H, Myles-Worsley M, et al. Linkage of a neurophysiological deficit in schizophrenia to a chromosome 15 locus. *Proc Natl Acad Sci U S A*. 1997;94:587–592.
 117. Myles-Worsley M, Coon H, Byerley W, Waldo M, Young D, Freedman R. Developmental and genetic influences on the P50 sensory gating phenotype. *Biol Psychiatry*. 1996;25:549–561.
 118. Patterson J, Jin Y, Gierczak M, et al. Effects of temporal variability on P50 and the gating ratio in schizophrenia: a frequency domain adaptive filter single-trial analysis. *Arch Gen Psychiatry*. 2000;57:57–64.
 119. Weiner E, Ball MP, Summerfelt A, Gold J, Buchanan R. Effects of sustained-release bupropion and supportive group therapy on cigarette consumption in patients with schizophrenia. *Am J Psychiatry*. 2001;158:635–637.
 120. Waldo MC, Graze K, De Graff Bender S, Adler LE, Freedman R. Premenstrual mood changes and gating of the auditory evoked potential. *Psychoneuroendocrinology*. 1987;12:35–40.
 121. Hall M-H, Schulze K, Rijdsdijk F, et al. Heritability and reliability of P300, P50 and duration mismatch negativity. *Behav Genet*. 2006;36:845–857.
 122. Young DA, Waldo M, Rutledge JH, Freedman R. Heritability of inhibitory gating of the P50 auditory-evoked potential in monozygotic and dizygotic twins. *Neuropsychobiology*. 2001;33:113–117.
 123. Leonard S, Gault J, Hopkins J, et al. Association of promoter variants in the alpha 7 nicotinic acetylcholine receptor subunit gene with an inhibitory deficit found in schizophrenia. *Arch Gen Psychiatry*. 2002;59:1085–1096.
 124. Raux G, Bonnet-Brilhault F, Louchart S, et al. The -2bp deletion in exon 6 of the alpha 7-like nicotinic receptor subunit

- gene is a risk factor for the P50 sensory gating deficit. *Mol Psychiatry*. 2002;7:1006–1011.
125. Houy E, Raux G, Thibaut F, et al. The promoter -194C polymorphism of the nicotinic alpha 7 receptor gene has a protective effect against the P50 sensory gating deficit. *Mol Psychiatry*. 2004;9:320–322.
 126. Thibaut F, Raux G, Bonnet-Brilhaut F, et al. P50 sensory gating deficit in schizophrenics and controls: the 2-bp deletion in Exon 6 of the alpha 7-like gene is a risk factor for the endophenotype. *Schizophr Res*. 2001;53:70.
 127. Hallett PE. Primary and secondary saccades to goals defined by instructions. *Vision Res*. 1978;18:1279–1296.
 128. McDowell JE, Myles-Worsley M, Coon H, Byerley W, Clementz BA. Measuring liability for schizophrenia using optimized antisaccade stimulus parameters. *Psychophysiology*. 1999;36:138–141.
 129. Matthews A, Flohr H, Everling S. Cortical activation associated with midtrial change of instruction in a saccade task. *Exp Brain Res*. 2002;143:488–498.
 130. Zhang M, Barash S. Persistent LIP activity in memory anti-saccades: working memory for a sensorimotor transformation. *J Neurophysiol*. 2004;91:1424–1441.
 131. Barash S, Zhang M. Switching of sensorimotor transformations: antisaccades and parietal cortex. *Novartis Found Symp*. 2006;270:59–71 discussion 71–74, 108–113.
 132. Guitton D, Buchtel HA, Douglas RM. Frontal lobe lesions in man cause difficulties in suppressing reflexive glances and in generating goal-directed saccades. *Exp Brain Res*. 1985;58:455–472.
 133. Johnston JL, Miller JD, Nath A. Ocular motor dysfunction in HIV-1-infected subjects: a quantitative oculographic analysis. *Neurology*. 1996;46:451–457.
 134. Everling S, DeSouza JF. Rule-dependent activity for prosaccades and antisaccades in the primate prefrontal cortex. *J Cogn Neurosci*. 2005;17:1483–1496.
 135. Pierrot-Deseilligny C, Muri RM, Nyffeler T, Milea D. The role of the human dorsolateral prefrontal cortex in ocular motor behavior. *Ann N Y Acad Sci*. 2005;1039:239–251.
 136. Ploner CJ, Gaymard BM, Rivaud-Pechoux S, Pierrot-Deseilligny C. The prefrontal substrate of reflexive saccade inhibition in humans. *Biol Psychiatry*. 2005;57:1159–1165.
 137. Amemori K, Sawaguchi T. Rule-dependent shifting of sensorimotor representation in the primate prefrontal cortex. *Eur J Neurosci*. 2006;23:1895–1909.
 138. Amador N, Schlag-Rey M, Schlag J. Primate antisaccade. II. Supplementary eye field neuronal activity predicts correct performance. *J Neurophysiol*. 2004;91:1672–1689.
 139. McDowell JE, Clementz BA. Behavioral and brain imaging studies of saccadic performance in schizophrenia. *Biol Psychol*. 2001;57:5–22.
 140. Raemaekers M, Jansma JM, Cahn W, et al. Neuronal substrate of the saccadic inhibition deficit in schizophrenia investigated with 3-dimensional event-related functional magnetic resonance imaging. *Arch Gen Psychiatry*. 2002;59:313–320.
 141. Gaymard B, Ploner CJ, Rivaud S, Vermersch AI, Pierrot-Deseilligny C. Cortical control of saccades. *Exp Brain Res*. 1998;123:159–163.
 142. Curtis CE, Calkins ME, Grove WM, Feil KJ, Iacono WG. Saccadic disinhibition in acute and remitted schizophrenia patients and their first-degree biological relatives. *Am J Psychiatry*. 2001;158:100–106.
 143. Clementz BA. Psychophysiological measures of (dis)inhibition as liability indicators for schizophrenia. *Psychophysiology*. 1998;35:648–668.
 144. McDowell JE, Brown GG, Paulus M, et al. Neural correlates of refixation saccades and antisaccades in normal and schizophrenia subjects. *Biol Psychiatry*. 2002;51:216–223.
 145. Nakashima Y, Momose T, Sano I, et al. Cortical control of saccade in normal and schizophrenic subjects: a PET study using a task-evoked rCBF paradigm. *Schizophr Res*. 1994;12:259–264.
 146. Klein C, Heinks T, Andresen B, Berg P, Moritz S. Impaired modulation of the saccadic contingent negative variation preceding antisaccades in schizophrenia. *Biol Psychiatry*. 2000;47:978–990.
 147. Bagary MS, Hutton SB, Symms MR, et al. Structural neural networks subserving oculomotor function in first-episode schizophrenia. *Biol Psychiatry*. 2004;56:620–627.
 148. Fukushima J, Fukushima K, Chiba T, Tanaka S, Yamashita I, Kato M. Disturbances of voluntary control of saccadic eye movements in schizophrenic patients. *Biol Psychiatry*. 1988;23:670–677.
 149. Ettinger U, Picchioni M, Hall MH, et al. Antisaccade performance in monozygotic twins discordant for schizophrenia: the Maudsley twin study. *Am J Psychiatry*. 2006;163:543–545.
 150. Ettinger U, Kumari V, Crawford TJ, et al. Smooth pursuit and antisaccade eye movements in siblings discordant for schizophrenia. *J Psychiatr Res*. 2004;38:177–184.
 151. Maccabe JH, Simon H, Zanelli JW, Walwyn R, McDonald CD, Murray RM. Saccadic distractibility is elevated in schizophrenia patients, but not in their unaffected relatives. *Psychol Med*. 2005;35:1727–1736.
 152. Kumari V, Ettinger U, Crawford TJ, Zachariah E, Sharma T. Lack of association between prepulse inhibition and antisaccadic deficits in chronic schizophrenia: implications for identification of schizophrenia endophenotypes. *J Psychiatr Res*. 2005;39:227–240.
 153. Louchart-de la Chapelle S, Nkam I, Houy E, et al. A concordance study of three electrophysiological measures in schizophrenia. *Am J Psychiatry*. 2005;162:466–474.
 154. Tendolkar I, Ruhrmann S, Brockhaus-Dumke A, et al. Neural correlates of visuo-spatial attention during an antisaccade task in schizophrenia: an ERP study. *Int J Neurosci*. 2005;115:681–698.
 155. Larrison-Faucher AL, Matorin AA, Sereno AB. Nicotine reduces antisaccade errors in task impaired schizophrenic subjects. *Prog Neuropsychopharmacol Biol Psychiatry*. 2004;28:505–516.
 156. Reuter B, Rakusan L, Kathmann N. Poor antisaccade performance in schizophrenia: an inhibition deficit? *Psychiatry Res*. 2005;135:1–10.
 157. Hutton SB, Huddy V, Barnes TR, et al. The relationship between antisaccades, smooth pursuit, and executive dysfunction in first-episode schizophrenia. *Biol Psychiatry*. 2004;56:553–559.
 158. Ettinger U, Kumari V, Chitnis XA, et al. Volumetric neural correlates of antisaccade eye movements in first-episode psychosis. *Am J Psychiatry*. 2004;161:1918–1921.
 159. Calkins ME, Curtis CE, Iacono WG, Grove WM. Antisaccade performance is impaired in medically and psychiatrically healthy biological relatives of schizophrenia patients. *Schizophr Res*. 2004;71:167–178.

160. Curtis CE, Calkins ME, Iacono WG. Saccadic disinhibition in schizophrenia patients and their first-degree biological relatives: a parametric study of the effects of increasing inhibitory load. *Exp Brain Res*. 2001;137:228–236.
161. McDowell JE, Clementz BA. The effect of fixation condition manipulations on antisaccade performance in schizophrenia: studies of diagnostic specificity. *Exp Brain Res*. 1997;115:333–344.
162. Broerse A, Holthausen EA, van den Bosch RJ, den Boer JA. Does frontal normality exist in schizophrenia? A saccadic eye movement study. *Psychiatry Res*. 2001;103:167–178.
163. Reuter B, Kathmann N. Using saccade tasks as a tool to analyze executive dysfunctions in schizophrenia. *Acta Psychol*. 2004;115:255–269.
164. Lee KH, Williams LM. Eye movement dysfunction as a biological marker of risk for schizophrenia. *Aust N Z J Psychiatry*. 2000;34:supplS91–S100.
165. Sweeney JA, Strojwas MH, Mann JJ, Thase ME. Prefrontal and cerebellar abnormalities in major depression: evidence from oculomotor studies. *Biol Psychiatry*. 1998;43:584–594.
166. Tien AY, Ross DE, Pearlson G, Strauss ME. Eye movements and psychopathology in schizophrenia and bipolar disorder. *J Nerv Ment Dis*. 1996;184:331–338.
167. Hutton S, Kennard C. Oculomotor abnormalities in schizophrenia: a critical review. *Neurology*. 1998;50:604–609.
168. Iacono WG. The genetics of psychopathology as a tool for understanding the brain: the search for a genetic marker of schizophrenia. In: Lieblisch I, ed. *Genetics of the Brain*. Amsterdam, The Netherlands: Elsevier; 1982:62–91.
169. Karoumi B, Ventre-Dominey J, Vighetto A, Dalery J, d'Amato T. Saccadic eye movements in schizophrenic patients. *Psychiatry Res*. 1998;77:9–19.
170. Ross RG, Harris JG, Olincy A, Radant A, Adler LE, Freedman R. Familial transmission of two independent saccadic abnormalities in schizophrenia. *Schizophr Res*. 1998;30:59–70.
171. Gooding DC, Shea HB, Matts CW. Saccadic performance in questionnaire-identified schizotypes over time. *Psychiatry Res*. 2005;133:173–186.
172. Gooding DC, Mohapatra L, Shea HB. Temporal stability of saccadic task performance in schizophrenia and bipolar patients. *Psychol Med*. 2004;34:921–932.
173. Calkins ME, Iacono WG, Curtis CE. Smooth pursuit and antisaccade performance evidence trait stability in schizophrenia patients and their relatives. *Int J Psychophysiol*. 2003;49:139–146.
174. Ettinger U, Kumari V, Crawford TJ, Davis RE, Sharma T, Corr PJ. Reliability of smooth pursuit, fixation, and saccadic eye movements. *Psychophysiology*. 2003;40:620–628.
175. Radant A, Dobie DJ, Calkins ME, et al. Successful multi-site measurement of antisaccade performance deficits in schizophrenia. *Schizophr Res*. 2006 Oct 2; [Epub ahead of print].
176. Thaker GK, Kirkpatrick B, Buchanan RW, Ellsberry R, Lahti A, Tamminga C. Oculomotor abnormalities and their clinical correlates in schizophrenia. *Psychopharmacol Bull*. 1989;25:491–497.
177. Thaker GK, Buchanan R, Kirkpatrick B, Tamminga CA. Oculomotor performance in schizophrenia. In: Schulz CS, Tamminga CA, eds. *Schizophrenia: Scientific Progress*. Oxford, UK: Oxford University Press; 1990:115–123.
178. Hutton SB, Joyce EM, Barnes TR, Kennard C. Saccadic distractibility in first-episode schizophrenia. *Neuropsychologia*. 2002;40:1729–1736.
179. Hutton SB, Crawford TJ, Puri BK, et al. Smooth pursuit and saccadic abnormalities in first-episode schizophrenia. *Psychol Med*. 1998;28:685–692.
180. Broerse A, Crawford TJ, den Boer JA. Differential effects of olanzapine and risperidone on cognition in schizophrenia? A saccadic eye movement study. *J Neuropsychiatry Clin Neurosci*. 2002;14:454–460.
181. Mahlberg R, Steinacher B, Mackert A, Flechtner KM. Basic parameters of saccadic eye movements—differences between unmedicated schizophrenia and affective disorder patients. *Eur Arch Psychiatry Clin Neurosci*. 2001;251:205–210.
182. Ettinger U, Kumari V, Zachariah E, et al. Effects of procyclidine on eye movements in schizophrenia. *Neuropsychopharmacology*. 2003;28:2199–2208.
183. Wonodi I, Adami H, Sherr J, Avila M, Hong LE, Thaker GK. Naltrexone treatment of tardive dyskinesia in patients with schizophrenia. *J Clin Psychopharmacol*. 2004;24:441–445.
184. Allen JS, Lambert AJ, Johnson FY, Schmidt K, Nero KL. Antisaccadic eye movements and attentional asymmetry in schizophrenia in three Pacific populations. *Acta Psychiatr Scand*. 1996;94:258–265.
185. Karoumi B, Saoud M, d'Amato T, et al. Poor performance in smooth pursuit and antisaccadic eye-movement tasks in healthy siblings of patients with schizophrenia. *Psychiatry Res*. 2001;101:209–219.
186. Nkam I, Thibaut F, Denise P, et al. Saccadic and smooth-pursuit eye movements in deficit and non-deficit schizophrenia. *Schizophr Res*. 2001;48:145–153.
187. Maruff P, Danckert J, Pantelis C, Currie J. Saccadic and attentional abnormalities in patients with schizophrenia. *Psychol Med*. 1998;28:1091–1100.
188. Depatie L, O'Driscoll GA, Holahan AL, et al. Nicotine and behavioral markers of risk for schizophrenia: a double-blind, placebo-controlled, cross-over study. *Neuropsychopharmacology*. 2002;27:1056–1070.
189. Burke JG, Reveley MA. Improved antisaccade performance with risperidone in schizophrenia. *J Neurol Neurosurg Psychiatry*. 2002;72:449–454.
190. Chaudhry IB, Soni SD, Hellewell JS, Deakin JF. Effects of the 5HT antagonist cyproheptadine on neuropsychological function in chronic schizophrenia. *Schizophr Res*. 2002;53:17–24.
191. Malone SM, Iacono WG. Error rate on the antisaccade task: heritability and developmental change in performance among preadolescent and late-adolescent female twin youth. *Psychophysiology*. 2002;39:664–673.
192. Brownstein J, Krastoshevsky O, McCollum C, et al. Antisaccade performance is abnormal in schizophrenia patients but not in their biological relatives. *Schizophr Res*. 2003;63:13–25.
193. Levy DL, O'Driscoll G, Matthyse S, Cook SR, Holzman PS, Mendell NR. Antisaccade performance in biological relatives of schizophrenia patients: a meta-analysis. *Schizophr Res*. 2004;71:113–125.
194. Myles-Worsley M, Coon H, McDowell J, et al. Linkage of a composite inhibitory phenotype to a chromosome 22q locus in eight Utah families. *Am J Med Genet*. 1999;88:544–550.
195. Egan MF, Goldberg TE, Kolachana BS, et al. Effect of COMT Val108/158 Met genotype on frontal lobe function and risk for schizophrenia. *Proc Natl Acad Sci U S A*. 2001;98:6917–6922.

196. Naatanen R, Paavilainen P, Alho K, Reinikainen K, Sams M. Do event-related potentials reveal the mechanism of the auditory sensory memory in the human brain? *Neurosci Lett*. 1989;98:217–221.
197. Gene-Cos N, Ring HA, Pottinger RC, Barrett G. Possible roles for mismatch negativity in neuropsychiatry. *Neuropsychiatry Neuropsychol Behav Neurol*. 1999;12:17–27.
198. Michie PT. What has MMN revealed about the auditory system in schizophrenia? *Int J Psychophysiol*. 2001;42:177–194.
199. Naatanen R. Mismatch negativity: clinical research and possible applications. *Int J Psychophysiol*. 2003;48:179–188.
200. Kathmann N, Frodl-Bauch T, Hegerl U. Stability of the mismatch negativity under different stimulus and attention conditions. *Clin Neurophysiol*. 1999;110:317–323.
201. Kujala T, Kallio J, Tervaniemi M, Naatanen R. The mismatch negativity as an index of temporal processing in audition. *Clin Neurophysiol*. 2001;112:1712–1719.
202. Pekkonen E, Rinne T, Naatanen R. Variability and replicability of the mismatch negativity. *Electroencephalogr Clin Neurophysiol*. 1995;96:546–554.
203. Light GA, Braff DL. Stability of mismatch negativity deficits and their relationship to functional impairments in chronic schizophrenia. *Am J Psychiatry*. 2005;162:1741–1743.
204. Naatanen R. *Attention and Brain Function*. Hillsdale, NJ: Lawrence Erlbaum Associates, Inc.; 1992.
205. Alho K, Sainio K, Sajaniemi N, Reinikainen K, Naatanen R. Event-related brain potential of human newborns to pitch change of an acoustic stimulus. *Electroencephalogr Clin Neurophysiol*. 1990;77:151–155.
206. Cheour-Luhtanen M, Alho K, Sainio K, et al. The ontogenetically earliest discriminative response of the human brain. *Psychophysiology*. 1996;33:478–481.
207. Huotilainen M, Kujala A, Hotakainen M, et al. Auditory magnetic responses of healthy newborns. *Neuroreport*. 2003;14:1871–1875.
208. Nashida T, Yabe H, Sato Y, et al. Automatic auditory information processing in sleep. *Sleep*. 2000;23:821–828.
209. Sabri M, Campbell KB. The effects of digital filtering on mismatch negativity in wakefulness and slow-wave sleep. *J Sleep Res*. 2002;11:123–127.
210. Fischer C, Morlet D, Bouchet P, Luaute J, Jourdan C, Salord F. Mismatch negativity and late auditory evoked potentials in comatose patients. *Clin Neurophysiol*. 1999;110:1601–1610.
211. Kane NM, Curry SH, Rowlands CA, et al. Event-related potentials—neurophysiological tools for predicting emergence and early outcome from traumatic coma. *Intensive Care Med*. 1996;22:39–46.
212. Morlet D, Bouchet P, Fischer C. Mismatch negativity and N100 monitoring: potential clinical value and methodological advances. *Audiol Neurootol*. 2000;5:198–206.
213. Binder LM, Kelly MP, Villanueva MR, Winslow MM. Motivation and neuropsychological test performance following mild head injury. *J Clin Exp Neuropsychol*. 2003;25:420–430.
214. Carrillo-de-la-Pena MT, Cadaveira F. The effect of motivational instructions on P300 amplitude. *Neurophysiol Clin*. 2000;30:232–239.
215. Pailing PE, Segalowitz SJ. The error-related negativity as a state and trait measure: motivation, personality, and ERPs in response to errors. *Psychophysiology*. 2004;41:84–95.
216. Perry W, Potterat EG, Braff DL. Self-monitoring enhances Wisconsin Card Sorting Test performance in patients with schizophrenia: performance is improved by simply asking patients to verbalize their sorting strategy. *J Int Neuropsychol Soc*. 2001;7:344–352.
217. Reitan RM, Wolfson D. Conation: a neglected aspect of neuropsychological functioning. *Arch Clin Neuropsychol*. 2000;15:443–453.
218. Reitan RM, Wolfson D. The differential effect of conation on intelligence test scores among brain-damaged and control subjects. *Arch Clin Neuropsychol*. 2004;19:29–35.
219. Braff DL, Light GA. Preattentive and attentional cognitive deficits as targets for treating schizophrenia. *Psychopharmacology*. 2004;174:75–85.
220. Alho K, Woods DL, Algazi A, Knight RT, Naatanen R. Lesions of frontal cortex diminish the auditory mismatch negativity. *Electroencephalogr Clin Neurophysiol*. 1994;91:353–362.
221. Baldeweg T, Klugman A, Gruzelier JH, Hirsch SR. Impairment in frontal but not temporal components of mismatch negativity in schizophrenia. *Int J Psychophysiol*. 2002;43:111–122.
222. Javitt DC, Steinschneider M, Schroeder CE, Vaughan HG Jr, Arezzo JC. Detection of stimulus deviance within primate primary auditory cortex: intracortical mechanisms of mismatch negativity (MMN) generation. *Brain Res*. 1994;667:192–200.
223. Kasai K, Nakagome K, Itoh K, et al. Multiple generators in the auditory automatic discrimination process in humans. *Neuroreport*. 1999;10:2267–2271.
224. Muller BW, Juptner M, Jentzen W, Muller SP. Cortical activation to auditory mismatch elicited by frequency deviant and complex novel sounds: a PET study. *Neuroimage*. 2002;17:231–239.
225. Naatanen R, Alho K. Generators of electrical and magnetic mismatch responses in humans. *Brain Topogr*. 1995;7:315–320.
226. Park HJ, Kwon JS, Youn T, et al. Statistical parametric mapping of LORETA using high density EEG and individual MRI: application to mismatch negativities in schizophrenia. *Hum Brain Mapp*. 2002;17:168–178.
227. Sato Y, Yabe H, Todd J, et al. Impairment in activation of a frontal attention-switch mechanism in schizophrenic patients. *Biol Psychol*. 2003;62:49–63.
228. Schairer KS, Gould HJ, Pousson MA. Source generators of mismatch negativity to multiple deviant stimulus types. *Brain Topogr*. 2001;14:117–130.
229. Schall U, Catts SV, Karayanidis F, Ward PB. Auditory event-related potential indices of fronto-temporal information processing in schizophrenia syndromes: valid outcome prediction of clozapine therapy in a three-year follow-up. *Int J Neuropsychopharmacol*. 1999;2:83–93.
230. Schall U, Johnston P, Todd J, Ward PB, Michie PT. Functional neuroanatomy of auditory mismatch processing: an event-related fMRI study of duration-deviant oddballs. *Neuroimage*. 2003;20:729–736.
231. Cheour M, Ceponiene R, Hukki J, Haapanen ML, Naatanen R, Alho K. Brain dysfunction in neonates with cleft palate revealed by the mismatch negativity. *Clin Neurophysiol*. 1999;110:324–328.
232. Cheour M, Haapanen ML, Ceponiene R, Hukki J, Ranta R, Naatanen R. Mismatch negativity (MMN) as an index of auditory sensory memory deficit in cleft-palate and CATCH syndrome children. *Neuroreport*. 1998;9:2709–2712.

233. Ilvonen TM, Kujala T, Kiesilainen A, et al. Auditory discrimination after left-hemisphere stroke. A mismatch negativity follow-up study. *Stroke*. 2003;34:1746–1751.
234. Jansson-Verkasalo E, Korpilahti P, Jantti V, et al. Neurophysiologic correlates of deficient phonological representations and object naming in prematurely born children. *Clin Neurophysiol*. 2004;115:179–187.
235. Kraus N, Micco AG, Koch DB, et al. The mismatch negativity cortical evoked potential elicited by speech in cochlear-implant users. *Hear Res*. 1993;65:118–124.
236. Javitt DC, Steinschneider M, Schroeder CE, Arezzo JC. Role of cortical N-methyl-D-aspartate receptors in auditory sensory memory and mismatch negativity generation: implications for schizophrenia. *Proc Natl Acad Sci U S A*. 1996;93:11962–11967.
237. Umbricht D, Schmid L, Koller R, Vollenweider FX, Hell D, Javitt DC. Ketamine-induced deficits in auditory and visual context-dependent processing in healthy volunteers: implications for models of cognitive deficits in schizophrenia. *Arch Gen Psychiatry*. 2000;57:1139–1147.
238. Umbricht D, Koller R, Vollenweider FX, Schmid L. Mismatch negativity predicts psychotic experiences induced by NMDA receptor antagonist in healthy volunteers. *Biol Psychiatry*. 2002;51:400–406.
239. Shelley AM, Ward PB, Catts SV, Michie PT, Andrews S, McConaghy N. Mismatch negativity: an index of a preattentive processing deficit in schizophrenia. *Biol Psychiatry*. 1991;30:1059–1062.
240. Umbricht D, Krljes S. Mismatch negativity in schizophrenia: a meta-analysis. *Schizophr Res*. 2005;76:1–23.
241. Catts SV, Shelley AM, Ward PB, et al. Brain potential evidence for an auditory sensory memory deficit in schizophrenia. *Am J Psychiatry*. 1995;152:213–219.
242. Umbricht D, Koller R, Schmid L, et al. How specific are deficits in mismatch negativity generation to schizophrenia? *Biol Psychiatry*. 2003;53:1120–1131.
243. Oades RD, Dittmann-Balcar A, Zerbin D, Grzella I. Impaired attention-dependent augmentation of MMN in non-paranoid vs paranoid schizophrenic patients: a comparison with obsessive-compulsive disorder and healthy subjects. *Biol Psychiatry*. 1997;41:1196–1210.
244. Oades RD, Zerbin D, Dittmann-Balcar A, Eggers C. Auditory event-related potential (ERP) and difference-wave topography in schizophrenic patients with/without active hallucinations and delusions: a comparison with young obsessive-compulsive disorder (OCD) and healthy subjects. *Int J Psychophysiol*. 1996;22:185–214.
245. Towey JP, Tenke CE, Bruder GE, et al. Brain event-related potential correlates of overfocused attention in obsessive-compulsive disorder. *Psychophysiology*. 1994;31:535–543.
246. van der Stelt O, Gunning WB, Snel J, Kok A. No electrocortical evidence of automatic mismatch dysfunction in children of alcoholics. *Alcohol Clin Exp Res*. 1997;21:569–575.
247. Tervaniemi M, Lehtokoski A, Sinkkonen J, Virtanen J, Ilmoniemi RJ, Naatanen R. Test-retest reliability of mismatch negativity for duration, frequency and intensity changes. *Clin Neurophysiol*. 1999;110:1388–1393.
248. Escera C, Yago E, Polo MD, Grau C. The individual replicability of mismatch negativity at short and long inter-stimulus intervals. *Clin Neurophysiol*. 2000;111:546–551.
249. Joutsiniemi SL, Ilvonen T, Sinkkonen J, et al. The mismatch negativity for duration decrement of auditory stimuli in healthy subjects. *Electroencephalogr Clin Neurophysiol*. 1998;108:154–159.
250. Umbricht D, Javitt D, Novak G, et al. Effects of clozapine on auditory event-related potentials in schizophrenia. *Biol Psychiatry*. 1998;44:716–725.
251. Umbricht D, Javitt D, Novak G, et al. Effects of risperidone on auditory event-related potentials in schizophrenia. *Int J Neuropsychopharmacol*. 1999;2:299–304.
252. Korostenskaja M, Dapsys K, Siurkute A, Maciulis V, Rukenas O, Kahkonen S. Effects of olanzapine on auditory P300 and mismatch negativity (MMN) in schizophrenia spectrum disorders. *Prog Neuropsychopharmacol Biol Psychiatry*. 2005;29:543–548.
253. Shinozaki N, Yabe H, Sato Y, et al. The difference in mismatch negativity between the acute and post-acute phase of schizophrenia. *Biol Psychol*. 2002;59:105–119.
254. Kawakubo Y, Kasai K. Support for an association between mismatch negativity and social functioning in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006;30:1367–1368.
255. Light GA, Braff DL. Mismatch negativity deficits are associated with poor functioning in schizophrenia patients. *Arch Gen Psychiatry*. 2005;62:127–136.
256. Siegel SJ, Connolly P, Liang Y, et al. Effects of strain, novelty, and NMDA blockade on auditory-evoked potentials in mice. *Neuropsychopharmacology*. 2003;28:675–682.
257. Jessen F, Fries T, Kucharski C, et al. Amplitude reduction of the mismatch negativity in first-degree relatives of patients with schizophrenia. *Neurosci Lett*. 2001;309:185–188.
258. Michie PT, Innes-Brown H, Todd J, Jablensky AV. Duration mismatch negativity in biological relatives of patients with schizophrenia spectrum disorders. *Biol Psychiatry*. 2002;52:749–758.
259. Bar-Haim Y, Marshall PJ, Fox NA, Schorr EA, Gordon-Salant S. Mismatch negativity in socially withdrawn children. *Biol Psychiatry*. 2003;54:17–24.
260. Schreiber H, Stolz-Born G, Kornhuber HH, Born J. Event-related potential correlates of impaired selective attention in children at high risk for schizophrenia. *Biol Psychiatry*. 1992;32:634–651.
261. Javitt DC, Shelley AM, Silipo G, Lieberman JA. Deficits in auditory and visual context-dependent processing in schizophrenia: defining the pattern. *Arch Gen Psychiatry*. 2000;57:1131–1137.
262. Umbricht DS, Bates JA, Lieberman JA, Kane JM, Javitt DC. Electrophysiological indices of automatic and controlled auditory information processing in first-episode, recent-onset and chronic schizophrenia. *Biol Psychiatry*. 2006;59:762–772.
263. Bramon E, Croft RJ, McDonald C, et al. Mismatch negativity in schizophrenia: a family study. *Schizophr Res*. 2004;67:1–10.
264. Salisbury DF, Shenton ME, Griggs CB, Bonner-Jackson A, McCarley RW. Mismatch negativity in chronic schizophrenia and first-episode schizophrenia. *Arch Gen Psychiatry*. 2002;59:686–694.
265. Brockhaus-Dumke A, Tendolkar I, Pukrop R, Schultze-Lutter F, Klosterkötter J, Ruhrmann S. Impaired mismatch negativity generation in prodromal subjects and patients with schizophrenia. *Schizophr Res*. 2005;73:297–310.
266. Cheour M, Haapanen ML, Hukki J, et al. The first neurophysiological evidence for cognitive brain dysfunctions in children with CATCH. *Neuroreport*. 1997;8:1785–1787.

267. Baker K, Baldeweg T, Sivagnanasundaram S, Scambler P, Skuse D. COMT Val108/158 Met modifies mismatch negativity and cognitive function in 22q11 deletion syndrome. *Biol Psychiatry*. 2005;58:23–31.
268. Glatt SJ, Faraone SV, Tsuang MT. Association between a functional catechol *O*-methyltransferase gene polymorphism and schizophrenia: meta-analysis of case-control and family-based studies. *Am J Psychiatry*. 2003;160:469–476.
269. Strous RD, Lapidus R, Viglin D, Kotler M, Lachman HM. Analysis of an association between the COMT polymorphism and clinical symptomatology in schizophrenia. *Neurosci Lett*. 2006;393:170–173.
270. Reinvang I, Espeseth T, Gjerstad L. Cognitive ERPs are related to ApoE allelic variation in mildly cognitively impaired patients. *Neurosci Lett*. 2005;382:346–351.
271. Regan D. *Human Brain Electrophysiology*. New York, NY: Elsevier Science Publishing; 1989.
272. Turetsky BI, Colbath EA, Gur RE. P300 subcomponent abnormalities in schizophrenia: I. Physiological evidence for gender and subtype specific differences in regional pathology. *Biol Psychiatry*. 1998;43:84–96.
273. Squires NK, Squires KC, Hillyard SA. Two varieties of long-latency positive waves evoked by unpredictable auditory stimuli in man. *Electroencephalogr Clin Neurophysiol*. 1975;38:387–340.
274. Halgren E, Squires NK, Wilson CL, Rohrbaugh JW, Babb TL, Crandall PH. Endogenous potentials generated in the human hippocampal formation and amygdala by infrequent events. *Science*. 1980;210:803–805.
275. Smith ME, Halgren E, Sokolik M, et al. The intracranial topography of the P3 event-related potential elicited during auditory oddball. *Electroencephalogr Clin Neurophysiol*. 1990;76:235–248.
276. Stapleton JM, Halgren E. Endogenous potentials evoked in simple cognitive tasks: depth components and task correlates. *Electroencephalogr Clin Neurophysiol*. 1987;67:44–52.
277. Kiehl KA, Laurens KR, Duty TL, Forster BB, Liddle PF. Neural sources involved in auditory target detection and novelty processing: an event-related fMRI study. *Psychophysiology*. 2001;38:133–142.
278. Yingling C, Hosobuchi Y. A subcortical correlate of P300 in man. *Electroencephalogr Clin Neurophysiol*. 1984;59:72–76.
279. McCarthy G, Wood CC. Intracranial recordings of endogenous ERPs in humans. In: Ellingson RJ, Murray NMF, Halliday AM, eds. *The London Symposia*. Amsterdam, The Netherlands: Elsevier Science; 1987:331–337.
280. Linden DEJ. The P300: where in the brain is it produced and what does it tell us? *Neuroscientist*. 2005;11:563–576.
281. Braff DL. Information processing and attention dysfunctions in schizophrenia. *Schizophr Bull*. 1993;19:233–259.
282. Duncan CC. Event-related brain potentials: a window on information processing in schizophrenia. *Schizophr Bull*. 1988;14:199–203.
283. Roth WT, Cannon FH. Some features of the auditory event-related response in schizophrenia. *Arch Gen Psychiatry*. 1972;27:466–471.
284. O'Donnell BF, Faux SF, McCarley RW, et al. Increased rate of P300 latency prolongation with age in schizophrenia. Electrophysiological evidence for a neurodegenerative process. *Arch Gen Psychiatry*. 1995;52:544–549.
285. Jeon YW, Polich J. Meta-analysis of P300 and schizophrenia: paradigms, and practical implications. *Psychophysiology*. 2003;40:684–701.
286. Blackwood DH, Whalley LJ, Christie JE, Blackburn IM, St Clair DM, McInnes A. Changes in auditory P3 event-related potential in schizophrenia and depression. *Br J Psychiatry*. 1987;150:154–160.
287. Saitoh O, Niwa S, Hiramatsu K, Kameyama T, Rymar K, Itoh K. Abnormalities in late positive components of event-related potentials may reflect a genetic predisposition to schizophrenia. *Biol Psychiatry*. 1984;19:293–303.
288. St Clair D, Blackwood D, Muir W. P300 abnormality in schizophrenic subtypes. *J Psychiatr Res*. 1989;23:49–55.
289. Turetsky BI, Colbath EA, Gur RE. P300 subcomponent abnormalities in schizophrenia: II. Longitudinal stability and relationship to symptom change. *Biol Psychiatry*. 1998;43:31–39.
290. Pfefferbaum A, Ford JM, White PM, Roth WT. P3 in schizophrenia is affected by stimulus modality, response requirements, medication status, and negative symptoms. *Arch Gen Psychiatry*. 1989;46:1035–1044.
291. McCarley RW, Faux SF, Shenton ME, Nestor PG, Adams J. Event-related potentials in schizophrenia: their biological and clinical correlates and a new model of schizophrenic pathophysiology. *Schizophr Res*. 1991;4:209–231.
292. Duncan CC, Morisha J, Fawcett R, Kirch D. P300 in schizophrenia: state or trait marker? *Psychopharmacol Bull*. 1987;23:497–501.
293. van der Stelt O, Lieberman JA, Belger A. Auditory P300 in high-risk, recent-onset and chronic schizophrenia. *Schizophr Res*. 2005;77:309–320.
294. Ford JM, White PM, Csernansky JG, Faustman WO, Roth WT, Pfefferbaum A. ERPs in schizophrenia: effects of antipsychotic medication. *Biol Psychiatry*. 1994;36:153–170.
295. Juckel G, Müller-Schubert A, Gaebel W, Hegerl U. Residual symptoms and P300 in schizophrenic outpatients. *Psychiatry Res*. 1996;65:23–32.
296. Mathalon DH, Ford JM, Pfefferbaum A. Trait and state aspects of P300 amplitude reduction in schizophrenia: a retrospective longitudinal study. *Biol Psychiatry*. 2000;47:434–449.
297. Faux SF, Torello MW, McCarley RW, Shenton ME, Duffy FH. P300 in schizophrenia: confirmation and statistical validation of temporal region deficit in P300 topography. *Biol Psychiatry*. 1988;23:776–790.
298. McCarley RW, Shenton ME, O'Donnell BF, et al. Auditory P300 abnormalities and left posterior superior temporal gyrus volume reduction in schizophrenia. *Arch Gen Psychiatry*. 1993;50:190–197.
299. Turetsky BI, Raz J, Alsop D, Charbonnier D, Schroeder L, Gur RE. Integrated ERP/fMRI analysis of deviance processing in schizophrenia. *Biol Psychiatry*. 2000;47:172S.
300. Grillon C, Courchesne E, Ameli R, Geyer MA, Braff DL. Increased distractibility in schizophrenic patients. Electrophysiologic and behavioral evidence. *Arch Gen Psychiatry*. 1990;47:171–179.
301. Ford JM, Sullivan EV, Marsh L, White PM, Lim KO, Pfefferbaum A. The relationship between P300 amplitude and regional gray matter volumes depends upon the attentional system engaged. *Electroencephalogr Clin Neurophysiol*. 1994;90:214–228.
302. Polich J, Ladish C, Bloom FE. P300 assessment of early Alzheimer's disease. *Electroencephalogr Clin Neurophysiol*. 1990;77:179–189.
303. Hesselbrock V, Begleiter H, Porjesz B, O'Connor S, Bauer L. P300 event-related potential amplitude as an endophenotype of alcoholism—evidence from the collaborative

- study on the genetics of alcoholism. *J Biomed Sci.* 2001;8:77–82.
304. Salisbury DF, Shenton ME, McCarley RW. P300 topography differs in schizophrenia and manic psychosis. *Biol Psychiatry.* 1999;45:98–106.
 305. Gangadhar BN, Ancy J, Janakiramaiah N, Umapathy C. P300 amplitude in non-bipolar, melancholic depression. *J Affect Disord.* 1993;28:57–60.
 306. Fabiani M, Gratton G, Karis D, Donchin E. Definition, identification and reliability of measurement of the P300 component of the event-related brain potential. In: Ackles PK, Jennings JR, Coles MGH, eds. *Advances in Psychophysiology.* London, England: JAI Press; 1986:1–78.
 307. Kileny PR, Kripal JP. Test-retest variability of auditory event-related potentials. *Ear Hear.* 1987;8:110–114.
 308. Kinoshita SM, Inoue M, Maeda H, Nakamura J, Morita K. Long-term patterns of change in ERPs across repeated measurements. *Physiol Behav.* 1996;60:1087–1092.
 309. Pollock VE, Schneider LS. Reliability of late positive component activity (P3) in healthy elderly adults. *J Gerontol.* 1992;47:M88–M92.
 310. Segalowitz SJ, Barnes KL. The reliability of ERP components in the auditory oddball paradigm. *Psychophysiology.* 1993;30:451–459.
 311. Sinha R, Bernardy N, Parsons OA. Long-term test-retest reliability of event-related potentials in normals and alcoholics. *Biol Psychiatry.* 1992;32:992–1003.
 312. Ford JM, Roth WT, Menod V, Pfefferbaum A. Failures of automatic and strategic processing in schizophrenia: comparisons of event-related brain potential and startle blink modification. *Schizophr Res.* 1998;37:149–163.
 313. Egan MF, Duncan CC, Suddath RL, Kirsh DG, Mirsky AF, Wyatt RJ. Event-related potential abnormalities correlate with structural brain alterations and clinical features in patients with chronic schizophrenia. *Schizophr Res.* 1994;11:259–271.
 314. Brown K, Gordon E, Williams L, et al. Misattribution of sensory input reflected in dysfunctional target: non-target ERPs in schizophrenia. *Psychol Med.* 2000;30:1443–1449.
 315. O'Connor S, Morzorati S, Christian JC, Li T-K. Heritable features of the auditory oddball event-related potential: peaks, latencies, morphology and topography. *Electroencephalogr Clin Neurophysiol.* 1994;92:115–125.
 316. Polich J, Burns T. P300 from identical twins. *Neuropsychologia.* 1987;25:299–304.
 317. Wright MJ, Hansell NK, Geffen GM, Geffen LB, Smith GA, Martin NG. Genetic influence on the variance in P3 amplitude and latency. *Behav Genet.* 2001;31:555–565.
 318. van Beijsterveldt CE, van Baal GC, Molenaar PC, Boomsma DI, de Geus EJ. Stability of genetic and environmental influences on P300 amplitude: a longitudinal study in adolescent twins. *Behav Genet.* 2001;31:533–543.
 319. Eischen SE, Polich J. P300 from families. *Electroencephalogr Clin Neurophysiol.* 1994;92:369–372.
 320. Rogers TD, Deary I. The P300 component of the auditory event-related potential in monozygotic and dizygotic twins. *Acta Psychiatr Scand.* 1991;83:412–416.
 321. Blackwood DHR, St Clair DM, Muir WJ, Duffy JC. Auditory P300 and eye tracking dysfunction in schizophrenic pedigrees. *Arch Gen Psychiatry.* 1991;48:899–909.
 322. Frangou S, Sharma T, Alarcon G, et al. The Maudsley Family Study, II: endogenous event-related potentials in familial schizophrenia. *Schizophr Res.* 1997;23:45–53.
 323. Karoumi B, Laurent A, Rosenfeld F, et al. Alteration of event related potentials in siblings discordant for schizophrenia. *Schizophr Res.* 2000;41:325–334.
 324. Kidogami Y, Yoneda H, Asaba H, Sakai T. P300 in first degree relatives of schizophrenics. *Schizophr Res.* 1992;6:9–13.
 325. Kimble M, Lyons M, O'Donnell B, Nestor P, Niznikiewicz M, Toomey R. The effect of family status and schizotypy on electrophysiologic measures of attention and semantic processing. *Biol Psychiatry.* 2000;47:402–412.
 326. Turetsky BI, Colbath EA, Gur RE. P300 subcomponent abnormalities in schizophrenia: III. Deficits in unaffected siblings of schizophrenic probands. *Biol Psychiatry.* 2000;47:380–390.
 327. Weisbrod M, Hill H, Niethammer R, Sauer H. Genetic influence on auditory information processing in schizophrenia: P300 in monozygotic twins. *Biol Psychiatry.* 1999;46:721–725.
 328. Cornblatt BA, Keilp JG. Impaired attention, genetics, and the pathophysiology of schizophrenia. *Schizophr Bull.* 1994;20:31–46.
 329. Winterer G, Egan MF, Raedler T, et al. P300 and genetic risk for schizophrenia. *Arch Gen Psychiatry.* 2003;60:1158–1167.
 330. Begleiter H, Porjesz B, Reich T, et al. Quantitative trait loci analysis of human event-related brain potentials: P3 voltage. *Electroencephalogr Clin Neurophysiol.* 1998;108:244–250.
 331. Porjesz B, Begleiter H, Wang K, et al. Linkage and linkage disequilibrium mapping of ERP and EEG phenotypes. *Biol Psychol.* 2002;61:229–248.
 332. Harrison PJ, Weinberger DR. Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry.* 2005;10:40–68.
 333. Hill SY, Locke J, Zezza N, et al. Genetic association between reduced P300 amplitude and the DRD2 dopamine receptor A1 allele in children at high risk for alcoholism. *Biol Psychiatry.* 1998;43:40–51.
 334. Mulert C, Juckel G, Giegling I, et al. A Ser9Gly polymorphism in the dopamine D3 receptor gene (DRD3) and event-related P300 potentials. *Neuropsychopharmacology.* 2006;31:1335–134.
 335. Blackwood DH, Fordyce A, Walker MT, St Clair DM, Porteous DJ, Muir W. Schizophrenia and affective disorders— cosegregation with a translocation at chromosome 1q42 that directly disrupts brain-expressed genes: clinical and P300 findings in a family. *Am J Hum Genet.* 2001;69:428–433.
 336. Swerdlow NR, Geyer MA, Shoemaker JM, et al. Convergence and divergence in the neurochemical regulation of prepulse inhibition of startle and N40 suppression in rats. *Neuropsychopharmacology.* 2006;31:506–515.
 337. Schwarzkopf SB, Lamberti JS, Smith DA. Concurrent assessment of acoustic startle and auditory P50 evoked potential measures of sensory inhibition. *Biol Psychiatry.* 1993;33:815–828.
 338. Braff DL, Light GA, Swerdlow NR. Prepulse inhibition and P50 suppression are both deficient but are not correlated in schizophrenia patients. *Biol Psychiatry.* In press.
 339. Calkins ME, Dobie DJ, Cadenhead KS, et al. The consortium on the genetics of endophenotypes in schizophrenia (COGS): “model” recruitment, assessment, and endophenotyping methods for a multi-site collaboration. *Schizophr Bull.* October 11, 2006. doi:10.1093/schbul/sbl044.