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Abnormal Auditory N100 Amplitude: A Heritable Endophenotype in First-Degree Relatives of Schizophrenia Probands

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Abstract

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Background—N100 evoked potential amplitude and gating abnormalities have been widely observed in schizophrenia patients. However, previous studies have been inconclusive as to whether similar deficits are present in unaffected family members. The Consortium on the Genetics of Schizophrenia (COGS) is a multi-site NIMH initiative examining neurocognitive and neurophysiological measures as endophenotypes for genetic studies of schizophrenia. We report initial results, from the COGS dataset, of auditory N100 amplitude and gating as candidate endophenotypes.

Methods—Evoked potential data were acquired from 142 schizophrenia probands, 373 unaffected 1st-degree relatives and 221 community comparison subjects (CCS), using an auditory paired-click stimulation paradigm. Amplitude of the N100 response to each click and the click2/click1 ratio were dependent variables. Heritability was estimated based on kinships, using Solar v.2.1.2. Group differences were examined after subjects were categorized as either “broad” or “narrow”, based on the presence (“broad”) or absence (“narrow”) of non-psychotic psychiatric co-morbidity.

Results—Heritability estimates were .40 and .29 for click1 and click2 amplitudes and .22 for the ratio. “Broad” and “narrow” patients both had impaired click1 amplitudes. “Broad” relatives, but not “narrow” relatives, exhibited similar impairments. There were no group differences for either click2 amplitude or the gating ratio.

Conclusions—N100 amplitude is a heritable measure that is abnormal in patients and a subset of relatives for whom psychiatric co-morbidity may be a genetically associated phenotype. Auditory N100 gating, although heritable, is less viable as a schizophrenia endophenotype.

Keywords

schizophrenia; endophenotype; heritability; evoked potential; N100; gating

Introduction

Genetic factors play an important role in the etiology of schizophrenia (1–5). However, phenocopies, genetic heterogeneity, diagnostic ambiguities, and polygenic inheritance complicate the genetic analysis of the illness (e.g.,6). Heritable physiological or behavioral traits, so-called endophenotypes, may offer a strategy to avoid the pitfalls of imprecise clinical phenotypes and facilitate genetic dissection (1,2,7–9).

To be an effective tool, endophenotypes must be both associated with illness in the population and be heritable. It should also be independent of clinical state and be manifest in unaffected family members at a higher rate than the general population (8). Reduced amplitude of the auditory N100 evoked potential is a robust physiological abnormality in schizophrenia (10, 11). N100 is an obligate response arising primarily from the auditory cortex approximately 100ms after presentation of an auditory stimulus (12). It is sensitive to physical characteristics of the stimulus (e.g., duration, intensity, rise time) (13), but less sensitive to contextual effects (e.g.,14) than later evoked potentials. Reduced N100 amplitude may reflect specific elements of schizophrenia pathophysiology, as distinct from those of other psychotic disorders (15).

Reduced gating of the N100 response to repeated stimulation has also been demonstrated in schizophrenia (16–19). This is typically observed as a larger S2/S1 amplitude ratio following paired stimulus presentation, although a smaller S1–S2 difference has occasionally been used as an alternate index (18,19). Although less well studied than P50 auditory gating (20), these N100 gating indices are more reliable measures (21,22) that may similarly reflect disturbed neuronal inhibitory processes in schizophrenia (18,23–25).

Although N100 amplitude and gating abnormalities have been observed repeatedly in schizophrenia, they have received little attention as potential endophenotypes. The data that

exist suggest that reduced N100 amplitude is a stable deficit found in both recent-onset (26) and medication-free (27) patients, that persists after both clinical stabilization and medication withdrawal (10). However, heritability of the N100 amplitude decrement and its status in unaffected family members of patients remain open questions. There is some evidence that reduced N100 amplitude is a heritable vulnerability factor and that the magnitude of the decrement correlates with the degree of genetic risk (28). However, 4 studies that contrasted first-degree relatives of schizophrenia patients with healthy comparison subjects failed to find any significant differences in N100 amplitude (29–32).

N100 gating, similarly, appears to be a stable deficit found in both medicated (18) and unmedicated (19) chronic patients. Based on a normative twin study (33), it also appears to be moderately heritable. However, its impairment in first-episode patients and prodromal individuals is more equivocal. In the one study that looked specifically at these subjects, no S2/S1 differences were found (19). To our knowledge, there have been no studies examining N100 gating deficits or their heritability in schizophrenia families.

This study presents the N100 amplitude and gating findings from the National Institute of Mental Health (NIMH) multi-site collaborative family study, the Consortium on the Genetics of Schizophrenia (COGS) (34; see <http://schizophreniaresearch.net/index.asp>). COGS is a 7-site project designed to conduct genetic analyses on neuropsychological and neurophysiological endophenotypic measures acquired from schizophrenia patients, their first-degree relatives and community comparison subjects (CCS). Data from this large cohort were used to compute heritability estimates and assess the magnitude of physiological impairments in patients and family members, to determine the viability of these measures as candidate endophenotypes.

Materials and Methods

Subject Ascertainment

Adults with and without schizophrenia were recruited through flyers, print and electronic media. Schizophrenia subjects were also ascertained by mental health providers and local chapters of the National Alliance on Mental Illness. Pedigrees were ascertained through the identified probands who met DSM-IV criteria for schizophrenia. The minimum requirement for pedigree ascertainment in COGS was a schizophrenia proband, two parents and one sibling unaffected with schizophrenia to provide DNA samples, and the proband and one unaffected sibling to participate in endophenotype assessments. Additional affected and unaffected family members participated when available. Schizophrenia subjects with only one available parent were enrolled if they had at least two siblings available for endophenotype and genotype assessment. Ascertainment criteria and screening procedures are discussed in detail by Calkins et al. (34). The local institutional review board at each site approved the study, and all subjects provided informed consent before commencing the study procedures.

2.2 Assessment

All subjects underwent a standardized diagnostic and clinical assessment that included a modified version of the Diagnostic Interview for Genetic Studies (DIGS) (35), the Family Interview for Genetic Studies (FIGS) (36), the Scale for Assessment of Negative Symptoms (37), the Scale for Assessment of Positive Symptoms (38), Mini-Mental State Exam (MMSE) (39) and a medical record review. Non-psychotic subjects received the Structured Interview for Schizotypy (SIS) (40). Interviewers were trained to administer these instruments by experienced COGS faculty members using a standardized training protocol. Each subject was assigned a DSM-IV best-estimate diagnosis through a consensus process that included at least 2 faculty-level clinicians.

The current sample included 142 unrelated schizophrenia probands, 373 unaffected first-degree relatives (130 parents, 243 siblings) and 221 unrelated community comparison subjects (CCS). All subjects were between the ages of 18–65, without hearing problems, and clinically stable for a minimum of one month. Patients and CCS were excluded for history of electroconvulsive therapy or substance dependence in the past 6 months, substance abuse in the past 30 days, estimated premorbid IQ less than 70, or history of severe head injury, seizure disorder, or other neurologic or systemic illness that could interfere with or compromise electrophysiological measurement. CCS were further excluded for a diagnosis of Cluster A Personality Disorder, personal or family history of psychosis (1st or 2nd degree relative), or current treatment with antipsychotic medications. For the current report, relatives were excluded for a personal history of psychosis, treatment with antipsychotic medications, severe head injury, or systemic illness that could compromise electrophysiologic measurement.

Subjects meeting these basic inclusion / exclusion criteria were further classified as “broad” or “narrow”, based on the presence (broad) or absence (narrow) of potential confounds that did not rise to the level of full exclusion. Schizophrenia patients were categorized as “broad” if they had a history of minor head injury, other Axis I disorder (except Adjustment Disorder), other non-exclusionary medical or neurological conditions, or more remote history of ECT, substance abuse or dependence. CCS were considered “broad” if they had a history of minor head injury, non-psychotic Axis I disorder, non-exclusionary medical or neurological condition, treatment with psychotropic medications, or remote substance abuse or dependence. “Broad” relatives were those with history of minor head injury, ECT, substance abuse or dependence, Axis I or Cluster A Personality Disorder diagnosis, non-exclusionary medical or neurological condition, past or current treatment with psychotropic medications, or IQ<70. Subjects without any of these modifying conditions were classified as “narrow”. Classification of all subjects as either “broad” or “narrow” was undertaken as part of the initial COGS consensus diagnostic process that preceded any examination of the electrophysiological data.

Demographic and clinical characteristics of the three groups are presented in Table 1, with first-degree relatives separated into parents and siblings. There were significant differences in gender [$\chi^2(2)=43.6$, $p<0.001$], age [$F(2,733)=33.95$, $p<.001$], education [$F(2,733)=28.21$, $p<.001$], parental education [$F(2,733)=5.40$, $p=.005$], MMSE [$F(2,733)=5.18$, $p=.006$] and broad vs. narrow classification [$\chi^2(2)=16.5$, $p<0.001$] across the three groups. The patient sample had a greater proportion of male subjects, lower education levels and lower MMSE scores than either the relatives or the CCS, who did not differ on any of these measures. Relatives were older than patients and CCS, which reflected the inclusion of parents in the relative group. When this sample was restricted to siblings, this age difference disappeared. The older parents of the schizophrenia probands also had lower parental education but, importantly, patients and controls did not differ on this measure. Finally, there was a greater prevalence of “broad” subjects in both the patient and relative samples than CCS, as would be expected given the inclusion criteria.

We therefore considered whether, independent of the proportion of subjects in the “broad” inclusion category, there were any differences, across groups, in the types of conditions that led to the “broad” designation. Table 2 presents the distribution of co-morbid conditions, along with a breakdown of different classes of psychotropic medications used by “broad” subjects. The distribution of co-morbid conditions was significantly different across groups [$\chi^2(12)=42.2$, $p<.001$]. However, in post-hoc contrasts, it was patients who differed significantly from the other groups. As might be expected, schizophrenia patients had greater prevalence of past substance-related disorders and lower prevalence of non-psychotic Axis I disorders. Importantly, there was no difference in the profile of co-morbid conditions between unaffected first-degree relatives and CCS [Bonferroni-corrected $p=.42$]. There was similarly no difference

in the proportion of relatives vs. CCS who were taking psychotropic medications [Fisher's Exact Test, $p=0.20$], or any specific class of medication. So, although the "broad" subjects had co-morbid conditions and treatments that could potentially affect electrophysiological brain measurements, the "broad" CCS and "broad" family members were quite similar to each other.

We also considered the relationship between this "broad" vs. "narrow" categorization and the degree of schizotypy, as assessed by the total score across all SIS global items, in relatives and CCS (see Table 1). As expected, relatives had higher SIS scores than CCS, independent of "broad" vs. "narrow" status [$F(1,567)=9.1$, $p=0.003$]. "Broad" subjects also had higher SIS scores than "narrow" subjects overall [$F(1,567)=33.3$, $p<0.001$]. In post-hoc contrasts, the "broad" vs. "narrow" difference was evident for both CCS [Bonferroni-corrected $p=0.012$] and relatives [Bonferroni-corrected $p<0.001$]. However, the CCS vs. relatives difference was not significant when considered separately within either the "broad" [Bonferroni-corrected $p=0.116$] or "narrow" [Bonferroni-corrected $p<0.382$] cohorts. The "broad"- "narrow" distinction therefore appeared to capture, to a large extent, the essential features of schizotypy within the non-psychotic sample.

2.3 Study design

An auditory evoked potential experiment originally designed to examine P50 gating - a primary dependent measure of the initial COGS proposal - was conducted as part of a broader research protocol that consisted of approximately 6 hours of neurocognitive and neurophysiological testing. The neurocognitive and neurophysiological tasks were presented in 2 standardized test orders. The equipment used for the auditory stimulus presentation and EEG data acquisition (LEA2003, Rave Wave Systems Inc.) was identical across study sites. Cross-site procedural consistency was maintained through annual training sessions, continuous data review by a single investigator responsible for quality assurance, and annual on-site inspections by a core staff research associate who acted as a subject at each site.

Auditory Stimulation

A 0.04-msec duration square wave pulse was amplified in the 20–12,000 Hz bandwidth and delivered through earphones to produce a 2.5-msec click stimulus. Mean stimulus intensity was independently set, for each ear, to 50 dB above the subject's monaural hearing threshold (41). Stimulus trials consisted of paired clicks presented with an intra-pair interval of 0.5 seconds and an inter-trial interval of 10 seconds. Subjects were seated in a reclining position and instructed to remain awake with eyes fixated on a distant target. Stimuli were delivered in 5 blocks, with each block containing a minimum of 16 click pairs. There was a brief 1–2 minute rest period between blocks.

Electrophysiological Recording

Electroencephalographic (EEG) activity was recorded from a gold disk electrode at the vertex (Cz) referenced to bilateral ear lobes. The EEG signal was amplified $\times 100,000$ with analog bandpass filter settings of 1 – 300 Hz ($\frac{1}{2}$ amplitude). The electro-oculogram (EOG) was recorded from electrodes at the right superior orbit and lateral canthus. For each stimulus trial, EEG and EOG data were digitally sampled at 1000Hz for 1000ms, beginning 100 ms prior to the first click.

EEG Data Processing

Digitized EEG and EOG recordings were bandpass filtered (1–50 Hz, 24 dB/octave) and corrected for eye blink artifacts using an established EOG correction algorithm (42). Individual trials with vertex minima or maxima exceeding $\pm 50\mu$ Volts were excluded prior to averaging. The average evoked potential waveform was baseline corrected relative to the 50 ms interval

preceding the first click. Figure 1 presents the grand average evoked potential waveforms for each subsample. N100 amplitude was measured as the minimum trough occurring 75ms–125ms after each stimulus. Dependent measures were N100 amplitudes following the first (S1) and second (S2) clicks and the S2/S1 ratio measure of N100 gating.

Statistical Analyses

Heritability—Separate heritability (h^2_r) estimates were obtained for each dependent measure using the variance component methodology implemented in the SOLAR v.2.1.2 linkage analysis package (43). Factors such as age and gender were assessed for their significance as covariates, and those showing a significant ($p < 0.05$) association with a dependent measure were retained in the heritability analysis for that measure. A correction was also made for ascertainment bias, since families were recruited through the identification of a proband with schizophrenia and were thus not representative of the general population (44).

Bivariate Correlations—Bivariate genetic (ρ_G) and environmental (ρ_E) correlations were computed using SOLAR (45,46). The genetic correlation between two measures is the component of the overall correlation that is due to pleiotropy (i.e., the influence of a gene or set of genes on both measures simultaneously), which is obtained from kinship information in the pedigree. The environmental correlation is the component of the correlation due to environmental factors that influence both measures, which is obtained from the individual-specific error.

Diagnosis Effects—Group differences were assessed using the Generalized Linear Latent and Mixed Models (GLLMM) algorithm implemented in Stata 9.0 (StataCorp; College Station, TX, USA), with subject, family and study site as hierarchically nested random-effects factors. This effectively accounted for any shared variance between individual members of the same family, and for differences across sites. Group (patient/relative/CCS), gender, age and clinical status (broad vs. narrow) were included as fixed-effects predictors of response. The significance levels of individual model parameters were assessed using the Wald test statistic with χ^2 distribution. Significant main effects and interactions were parsed by post-hoc computation of appropriate linear combinations of the model coefficients, along with their associated z-statistic and p-value. Post-hoc contrasts were subject to Bonferroni corrected p-values of $p < .05$ to avoid Type I errors from multiple comparisons.

Results

Heritability

Heritability estimates are presented in Table 3. All dependent measures exhibited statistically significant heritability, with S1 being the most and S2/S1 the least heritable. Age and gender were significant covariates for S1, but not S2.

Bivariate Correlations

Table 4A presents the bivariate Pearson correlations for the 3 dependent measures, for the total sample and separately within each diagnostic group. There was a moderate association between S1 and S2, which was comparable across the three groups. S2/S1 was more strongly correlated with S2 than S1, particularly among patients and family members.

Bivariate environmental (Table 4B) and genetic (Table 4C) correlations are estimates of the strengths of the components of the observed correlations that can be attributed to either environmental or genetic factors, based on kinship information. There was a significant shared environmental contribution to each of the bivariate associations. There was also a significant genetic correlation ($\rho_G > 0$) between S1 and S2, indicating a shared genetic substrate. Although

this genetic correlation was relatively strong, it did not reflect complete pleiotropy [i.e., $\rho_G < 1.0, p=0.04$]. So there are likely independent, as well as shared, genes that contribute to each measure. Importantly, there was no genetic association between S2/S1 and either S1 or S2, indicating that N100 amplitude and gating - while both heritable - are genetically independent.

Group Differences

Mean values ($\pm$ s.d.) for each dependent measure, separated by group, are presented in Table 5. For S1, there were significant main effects of gender [$\chi^2(1)=17.30, p<0.0001$], age [$\chi^2(1)=14.24, p<0.001$] and diagnostic group [$\chi^2(2)=12.32, p=0.002$]. Responses were larger in women and decreased with increasing age. Patients had smaller S1 responses than both CCS [$\chi^2(1)=10.66, p=0.001$] and family members [$\chi^2(1)=8.97, p=0.003$], who did not differ [$\chi^2(1)=0.66, p=0.417$]. There were also a significant two-way interaction of group X clinical status (broad vs.narrow) [$\chi^2(2)=14.63, p<0.001$]. In paired contrasts, clinical status was a significant moderating variable for the comparison between family members and CCS [$\chi^2(1)=10.39, p=0.001$], but not for patient – CCS differences [$\chi^2(1)=0.01, p=0.937$]. Family members had reduced N100 amplitudes only within the "broad" clinical status category. "Narrow" family members were indistinguishable from "narrow" comparison subjects. Figure 2 presents the group means ($\pm$ s.e.) for each dependent measure. Effect sizes (Cohen's d) and associated p-values are included for each paired contrasts of patients vs. CCS and relatives vs. CCS. Significant effects ranged from $d=0.39$ for the "narrow" patient S1 amplitude decrement to $d=0.46$ for the "broad" family member S1 amplitude decrement, indicating a moderate range of effect sizes (47). There were no significant main or interaction effects for S2. For S2/S1, there was only a significant age effect [$\chi^2(1)=4.06, p=0.044$], with increasing age associated with decreased gating. However, there were no group differences on this measure.

Given the association between increased age and decreased N100 amplitude, we considered the possibility that the increased age of the family members may have spuriously contributed to their observed N100 amplitude decrement, despite the inclusion of age in the statistical model. We therefore repeated the group analysis using only siblings, who were comparable in age to CCS, rather than siblings plus parents. The results were identical. Despite the reduced sample size, all previously significant effects were reproduced and no new significant effects emerged. We also considered other factors that may have contributed to the "broad" family member decrement. Psychotropic medication use was not a significant mediating variable [medicated relatives: $\chi^2(1)=4.44, p=0.035$; unmedicated relatives: $\chi^2(1)=8.41, p=0.004$]. However, the specific condition underlying the "broad" categorization was important. In separate analyses, we compared CCS and relatives when the samples were restricted to either those with substance use disorders or those with other non-psychotic Axis I diagnoses – the two major "broad" categories. As illustrated in Figure 3, there was a significant CCS - relatives difference among those with non-psychotic Axis I diagnoses [$\chi^2(1)=7.53, p=0.006$], but not among those with substance use disorders [$\chi^2(1)=0.08, p=0.773$].

Discussion

These findings support two basic conclusions: 1) N100 amplitude is a robust heritable trait; 2) Reduced N100 amplitude, which has been observed repeatedly in schizophrenia patients, is also present in a subset of unaffected first-degree relatives. This simple measure of auditory sensory processing therefore appears to meet two essential criteria of a viable endophenotype for genetic studies. A similar conclusion can not be drawn for N100 gating. Although the gating measure was heritable, it was not abnormal in either schizophrenia patients or their unaffected family members. However, given our finding of reduced S1 but normal S2 amplitude, we cannot entirely rule out the possibility of two opposing abnormalities - impaired excitation of

the N100 cortical generator and impaired gating of the response to repeated stimulation - despite the lack of a significant S2/S1 difference.

It is notable that a familial N100 amplitude deficit was not apparent when the entire first-degree relative sample was contrasted with the entire CCS sample. The familial deficit emerged only when subjects were separated into those with or without co-morbid psychiatric or substance use conditions. Family members with co-morbid conditions had reduced N100 amplitudes relative to CCS with similar co-morbidity. Indeed, in this group, the familial impairment was equal to that seen in patients. However, family members without co-morbidity were indistinguishable from CCS without similar co-morbidity. Importantly, although the presence of co-morbid conditions was associated with reduced N100 amplitude in family members, there was no similar reduction associated with co-morbidity in CCS. One explanation for this pattern of findings is that the presence of psychiatric co-morbidity effectively identified those unaffected family members who carried the highest genetic loading for schizophrenia vulnerability. This would be consistent with our findings that 1) "broad" family members who had co-morbid conditions also had the highest ratings of schizotypy, and 2) among the "broad" family members, it was specifically those with other Axis I diagnoses (i.e., mood and anxiety disorders) who differed from comparable CCS. In the absence of other psychiatric co-morbidity, substance use may be more environmentally influenced and, therefore, less strongly associated with genetic vulnerability to schizophrenia. An alternative explanation is that the genetic risk of schizophrenia was comparable in both "broad" and "narrow" relatives, but that the joint effect of schizophrenia vulnerability and co-morbid conditions resulted in a significant N100 decrement. We consider this explanation less likely, as we would then expect to see evidence of smaller independent effects of psychiatric co-morbidity in the "broad" CCS and genetic vulnerability in the "narrow" family members, neither of which was present.

As noted above, four of five previous studies of N100 amplitude in unaffected family members (28–32) reported normal responses in the relatives. Our sample, which was obtained from seven collaborating sites nationwide, was larger and therefore had more power to detect small effects. Nevertheless, we also had normal responses in our unaffected family member sample as a whole. The critical difference between this and previous studies was that we did not assume that family members were all the same and therefore could be grouped together for analyses. Unaffected family members are known to have an increased prevalence of behavioral and psychiatric conditions other than schizophrenia (48–50). We therefore adopted a very liberal set of inclusion criteria for these subjects and recruited a similarly broad sample of CCS. Most importantly, we considered these co-morbid conditions to potentially represent associated phenotypes within the at-risk sample and therefore split the sample based on the presence or absence of these co-morbid conditions. Previous studies tended to either exclude family members with history of other Axis I psychiatric disorders or substance abuse (e.g., 29,30), or to group them together with relatives without these conditions (e.g., 31). If, as our data suggest, these co-morbid conditions are not independent of genetic vulnerability then excluding carriers, or co-mingling carriers and non-carriers, would necessarily reduce the power to detect significant differences.

There are, however, reasons to believe that our observed effect sizes are at the low end of what might be expected for N100 amplitude. The COGS database likely reflects an ascertainment bias that skewed the composition of the sample. The COGS design required that both parents and one healthy sibling of each patient proband participate in the research. This necessarily selected for both family members and patients who maintained a cohesive relationship with each other and were motivated to participate in an extensive experimental protocol. This cohort likely represents a somewhat atypical and less severe manifestation of the illness. This ascertainment bias probably also contributed to our failure to observe an N100 gating deficit.

Our CCS sample exhibited S2/S1 ratios that closely mirrored previous published values (22), but our patients had substantially lower ratios (18,19).

In addition, the stimulus protocol that we employed was designed to investigate P50 auditory gating, not N100 amplitude. Typical N100 studies use pure tone stimuli of substantially longer duration (e.g., 50ms), shorter inter-stimulus intervals (ISI) (e.g., 1–2 seconds) and tasks that require subjects to attend to the stimuli (e.g., target detection tasks). Under these conditions, the effect size of the N100 amplitude decrement in patients is typically around 1.0 (e.g., 15, 51). It is likely that physical stimulus characteristics and task demands are more critical than inter-stimulus interval. Studies of N100 recovery cycle (23–25) have consistently demonstrated schizophrenia decrements at all ISIs > 1.5–2.0 seconds and normal responses at ISIs < 0.5–1.0 seconds. Within the range of 2.0–10.0 second ISI, N100 amplitudes tend to increase with longer ISI, but patient decrements remain relatively constant. However, an experimental protocol in which subjects attended to longer duration pure tones would produce more robust N100 decrements than those observed here.

It is important to emphasize that, beyond its utility as a quantitative endophenotype for human genetic studies, the auditory N100 also provides a way to investigate the neural substrates of schizophrenia. This evoked potential abnormality reflects impairment in early auditory sensory processing localized to primary and secondary auditory cortex (52). Analogous responses can be elicited in simple mouse models, allowing both its neurochemical and genetic underpinnings to be explored via pharmacological probes and/or reverse genetic strategies (e.g., 53). This will be especially important as we strive to move beyond the initial identification of schizophrenia candidate genes to a fuller understanding of their functional significance (2,9,34).

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Figure 1.

Grand average evoked potential waveforms for schizophrenia patients and CCS (top) and unaffected family members and CCS (bottom). Left: "broad" clinical sample with co-morbid psychiatric conditions; Right: "narrow" clinical sample with no co-morbidity. The N100 evoked potential component is the distinct trough at 100 ms (S1) and 600 ms (S2).

Figure 2. Mean ($\pm$ s.e.) N100 responses for patients, unaffected family members and CCS segregated by "broad" (left) and "narrow" (right) clinical status. Top: Click 1 amplitude (S1); Middle: Click 2 amplitude (S2); Bottom: Gating ratio (S2/S1). Effect size (Cohen's d) and associated significance level is indicated for each patient vs. CCS and family member vs. CCS comparison.

Figure 3.

Mean ($\pm$ s.e.) S1 N100 responses for “broad” unaffected family members and “broad” CCS, segregated into those with substance use disorders (left) and those with other non-psychotic Axis I diagnoses. Effect size (Cohen's d) and associated significance level is indicated for each family member vs. CCS comparison.

Table 1

Sample Characteristics

			Relatives	
	Patients	CCS	Parents	Siblings
<u>Gender</u>				
Male #	103 (72%)	97 (44%)	52 (40%)	100 (41%)
Female #	39 (28%)	124 (56%)	79 (60%)	142 (59%)
<u>Age (years)</u>				
Range	18–62	18–64	40–65	18–64
Mean (sd)	35.2 (11.2)	36.7 (12.1)	55.5 (5.1)	37.1 (11.5)
<u>Education (years)</u>				
Mean (sd)	13.6 (2.2)	15.4 (2.7)	15.4 (3.2)	15.5 (2.5)
<u>Parental Education (years)</u>				
Mean (sd)	14.8 (3.0)	14.2 (2.7)	12.0 (3.4)	14.6 (3.0)
<u>Mini Mental Status Exam (0–35)</u>				
Mean (sd)	32.9 (6.7)	34.1 (1.4)	33.9 (2.0)	34.0 (2.3)
<u>Broad vs. Narrow Clinical Status</u>				
Broad #	58 (41%)	68 (31%)	64 (49%)	114 (47%)
Narrow #	84 (59%)	153 (69%)	67 (51%)	128 (53%)
<u>Structured Interview for Schizotypy (Mean, sd)</u>				
Total Sample	N/A	9.9 (7.0)	11.6 (7.6)	12.7 (7.5)
Broad Subjects	N/A	12.1 (7.3)	13.9 (8.3)	14.9 (8.2)
Narrow Subjects	N/A	8.9 (6.7)	9.5 (6.2)	10.8 (6.3)

Statistical outliers for each measure are highlighted in **bold**. See text for details.

CCS = Community Comparison Subjects

Table 2

“Broad” Sample Characteristics

	Patients		CCS		Relatives	
	#	%	#	%	#	%
Co-Morbid Conditions						
Substance Abuse	17	29.3	10	14.7	24	13.8
Substance Dependence	19	32.8	13	19.1	17	9.6
Head Injury	3	5.2	4	5.9	10	5.6
Non-Psychotic Axis I Disorder	9	15.5	26	38.2	95	53.4
Medical / Neurological Illness	0	0.0	0	0.0	4	2.2
Other Conditions	3	5.2	7	10.3	9	5.1
Multiple Conditions	7	12.1	8	11.8	19	10.7
Psychotropic Medications*						
Antipsychotics	133	93.6	0	0.0	0	0.0
Antidepressants	23	39.7	9	13.2	38	21.3
Mood Stabilizers	6	10.3	0	0.0	10	5.6
Anxiolytics / Sedative Hypnotics	12	20.7	4	5.9	15	8.4
Stimulants	0	0.0	0	0	2	1.1

* Subjects taking more than 1 medication are counted in each agent class.

CCS = Community Comparison Subjects

Table 3

Heritability Estimates (h^2_r)

Measure	h^2_r	SE	P value	Covariate P Values	
				Age	Gender
Click 1 Amplitude (S1)	0.40	0.10	<0.0001	0.0001	0.0001
Click 2 Amplitude (S2)	0.29	0.09	0.0007	0.271	0.350
Click 2 / Click 1 Ratio (S2/S1)	0.22	0.10	0.011	0.003	0.253

Table 4

Bivariate Correlations

A. Pearson Correlations (r)									
Total Sample			Patients			CCS		Relatives	
Measure	S1	S2	S1	S2	S1	S1	S2	S1	S2
S2	.381**		.449**		.403**			.346**	
S2/S1	-.259**	.513**	-.172*	.591**	-.328**		.375**	-.238**	.602**

B. Environmental Correlations (p _E)			
Measure	S1 Amplitude	S2 Amplitude	
S2 Amplitude	0.21 ± 0.10 (0.036)		
S2/S1 Ratio	-0.33 ± 0.09 (0.002)	0.65 ± 0.06 (<0.0001)	

C. Genetic Correlations (p _G)			
Measure	S1 Amplitude	S2 Amplitude	
S2 Amplitude	0.63 ± 0.20 (0.006)		
S2/S1 Ratio	-0.36 ± 0.21 (0.143)	0.60 ± 0.18 (0.067)	

** p<0.05
* p<0.001

Environmental and genetic correlation statistics are presented ± standard error (p value)

Table 5

N100 Amplitude and Gating Measures Mean ± S.D

	"Broad" Sample				"Narrow" Sample				Total Sample			
	Patients (N=58)	Relatives (N=178)	CCS (N=68)	Patients (N=84)	Relatives (N=195)	CCS (N=153)	Patients (N=142)	Relatives (N=373)	CCS (N=221)	Patients (N=142)	Relatives (N=373)	CCS (N=221)
S1	7.46±3.82	7.28±3.94	9.24±4.66	6.80±3.96	9.05±4.47	8.41±4.28	7.07±3.90	8.20±4.31	8.66±4.40	7.07±3.90	8.20±4.31	8.66±4.40
S2	2.66±1.66	2.64±1.77	3.05±1.87	2.66±2.21	2.79±1.90	2.64±1.97	2.66±2.00	2.72±1.84	2.76±1.95	2.66±2.00	2.72±1.84	2.76±1.95
S2/S1	0.41±0.29	0.43±0.35	0.37±0.37	0.43±0.58	0.35±0.29	0.38±0.48	0.42±0.48	0.39±0.32	0.37±0.45	0.42±0.48	0.39±0.32	0.37±0.45