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### Title

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### Permalink

<https://escholarship.org/uc/item/5k35x8bw>

### Journal

The American journal of psychiatry, 173(4)

### ISSN

0002-953X

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### Publication Date

2016-04-01

### DOI

10.1176/appi.ajp.2015.15050605

Peer reviewed

# Gating Deficit Heritability and Correlation With Increased Clinical Severity in Schizophrenia Patients With Positive Family History

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**Objective:** The Consortium on the Genetics of Schizophrenia Family Study evaluated 12 primary and other supplementary neurocognitive and neurophysiological endophenotypes in schizophrenia probands and their families. Previous analyses of prepulse inhibition (PPI) and P50 gating measures in this sample revealed heritability estimates that were lower than expected based on earlier family studies. Here the authors investigated whether gating measures were more heritable in multiply affected families with a positive family history compared with families with only a single affected proband (singleton).

**Method:** A total of 296 nuclear families consisting of a schizophrenia proband, at least one unaffected sibling, and both parents underwent a comprehensive endophenotype and clinical characterization. The Family Interview for Genetic Studies was administered to all participants and used to obtain convergent psychiatric symptom information for additional first-degree relatives. Among the families, 97 were multiply affected, and 96 were singletons.

**Results:** Both PPI and P50 gating displayed substantially increased heritability in the 97 multiply affected families (47% and 36%, respectively) compared with estimates derived from the entire sample of 296 families (29% and 20%, respectively). However, no evidence for heritability was observed for either measure in the 96 singleton families. Schizophrenia probands derived from the multiply affected families also displayed a significantly increased severity of clinical symptoms compared with those from singleton families.

**Conclusions:** PPI and P50 gating measures demonstrate substantially increased heritability in schizophrenia families with a higher genetic vulnerability for illness, providing further support for the commonality of genes underlying both schizophrenia and gating measures.

*Am J Psychiatry* 2016; 173:385–391; doi: 10.1176/appi.ajp.2015.15050605

Schizophrenia is a clinically heterogeneous disorder in which patients exhibit a broad range of deficits and symptom severity. A core feature of the illness is a fundamental impairment in the ability to filter sensory information (1, 2), and the complex cognitive deficits in attention, information processing, learning, and memory that also characterize schizophrenia may arise from these primary deficits in sensory processing, or “gating.” Intact gating processes allow healthy individuals to filter out irrelevant stimuli and appropriately allocate attentional resources. However, impaired gating in schizophrenia patients may lead to sensory overload, distorted perceptions, and cognitive fragmentation (3). Misinterpretations of a cascade of irrelevant stimuli may further result in some of the observed symptoms associated with schizophrenia, such as hallucinations, delusions,

disorganized speech and thought, and social awkwardness (1, 2, 4–6).

Prepulse inhibition (PPI) and P50 gating are neurophysiological endophenotypes for schizophrenia that reflect inhibitory abnormalities in central gating processes. PPI is an index of sensorimotor gating measured as a reduction in the acoustic startle response magnitude that occurs when the intense startling pulse stimulus is preceded 30–300 ms by a weak prepulse (7–9). The P50 wave is a midlatency auditory evoked potential that exhibits reduced amplitude when a second (test) click is presented 500 ms after an initial (conditioning) click in a paired-click paradigm (2). The PPI and P50 deficits observed in schizophrenia patients extend to their clinically unaffected relatives, as well as to schizotypal

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individuals and adolescents at high risk for schizophrenia, indicating that these deficits are present across the schizophrenia spectrum and may be biomarkers for genetic risk for the disorder (1, 6, 10–21). Although PPI and P50 measures are conceptually linked to gating processes, evidence directly connecting these measures to sensory overload, distorted perceptions, or cognitive fragmentation is currently lacking. Evidence does suggest, however, that these two measures detect distinct aspects of pathophysiology that may be characteristic of different subgroups of patients (22–26).

The Consortium on the Genetics of Schizophrenia (COGS) explores neurophysiological and neurocognitive endophenotypes as a means to understand the neurobiological processes underlying schizophrenia. We have previously reported significant heritability for 12 primary endophenotypes in the COGS Family Study (COGS-1). These analyses revealed estimates of heritability for PPI and P50 gating that were significant but modest compared with earlier family studies of these measures (27–32). COGS-1 focused on the recruitment of discordant sib pairs and intact families available for extensive testing in order to maximize the potential for phenotypic contrasts between and within families. We speculated that this ascertainment strategy might have also created a downward pressure on the estimated heritability of certain endophenotypes through the recruitment of probands with nonfamilial (i.e., sporadic) forms of schizophrenia (33–35). The heritability of PPI and P50 measures in particular may have been affected, as they reflect primary gating deficits in schizophrenia. Here we report the evaluation of the heritability of PPI and P50 gating separately in families with a positive family history for schizophrenia and related disorders derived from multiple affected family members (multiply affected) compared with families containing only the proband affected with schizophrenia and no other family members with any major psychiatric illness (singleton). These heritability estimates were compared with those generated from the entire COGS-1 sample to test the hypothesis that family history substantially and specifically affects the heritability of gating measures.

## METHOD

### Subjects

Families were ascertained at seven sites through the identification of probands who met DSM-IV-TR criteria for schizophrenia. Each family consisted of a proband with schizophrenia, at least one unaffected sibling, and both parents. Families in which both parents were affected with schizophrenia were considered ineligible because of the complexities of bilineal transmission patterns. Blood samples were required for all subjects, and endophenotypes were required for the proband and unaffected sibling at minimum. Additional affected and unaffected siblings were included whenever possible, and families missing one or both parents were accepted if one or two additional siblings were available for testing. The ascertainment and screening procedures and

inclusion and exclusion criteria have been discussed in detail elsewhere (33). The final COGS-1 data set as described here included 296 nuclear families with an average family size of 4.6 members. The majority of families (62%) consisted of a single sibling pair discordant for schizophrenia, with sibships of three accounting for 26% of families and larger sibships accounting for 12% of families. Healthy subjects were also recruited for comparison and similarly screened.

Diagnoses for all 1,297 participating subjects were obtained via the administration of the Diagnostic Interview for Genetic Studies (36). The Family Interview for Genetic Studies was also administered to all participants to obtain convergent psychiatric diagnoses for first-degree relatives of interviewed participants (37). Using the Family Interview for Genetic Studies information from reliable first-degree informants and best-estimate consensus diagnostic procedures, we were able to extend the nuclear families to comprise 3,303 subjects and obtain convergent psychiatric diagnoses for 1,952 additional first-degree relatives of interviewed participants who did not participate in endophenotype testing (Table 1). We then evaluated families for the presence or absence of family history of schizophrenia or related disorders. Given the presumed genetic relationships between these disorders, families with two or more members having diagnoses of schizophrenia and/or bipolar disorder were considered as multiply affected with a positive family history (38). Families in which there were no other members having diagnoses of schizophrenia, bipolar disorder, or major depression beyond the schizophrenia proband were considered as singleton families with a negative family history. Families with additional members having diagnoses of major depression only in addition to the schizophrenia proband were considered as having indeterminate family history and were removed from further consideration. A complete description of this process is available elsewhere (35).

Endophenotyped subjects ranged in age from 18 to 65 and received urine toxicology screens for drugs of abuse prior to assessment (negative screens and histories of recent abuse were required). PPI was measured as the percent inhibition of the startle reflex in response to a weak prestimulus using a 60-ms prepulse interval (7, 9, 15, 39). While PPI was our primary startle endophenotype, we also assessed pulse-alone startle magnitude on nonprepulse trials for comparison. P50 gating was measured as the difference in amplitudes of the P50 event-related potentials generated in response to the conditioning (S1) and test (S2) stimuli that are presented with a 500-ms interstimulus interval (14, 40, 41). The S1 and S2 amplitudes were also considered individually for comparison with the gating measures. To test whether the impact of family history may be specific to gating measures, we further evaluated the three primary cognitive endophenotypes from COGS-1: the Degraded Stimulus Continuous Performance Test ( $d'$  measure), the Letter-Number Span (reordered condition), and the California Verbal Learning Test (list A total score summed over five trials). Clinical symptom severity in the probands was assessed using the Scale for the Assessment

of Negative Symptoms (SANS) and the Scale for the Assessment of Positive Symptoms (SAPS) (42, 43). A modified Global Assessment of Functioning Scale (GAF) was used to assess the overall level of functional status across psychological, social, and occupational domains via an anchored measure (44).

### Statistical Analyses

Variance components methods in the SOLAR software package, version 4.3.1 (<http://solar.txbiomedgenetics.org/>), were used to estimate the narrow sense heritability for each endophenotype, defined as the phenotypic variance explained by additive genetic factors (45). The distribution of values for each endophenotype was examined prior to analysis to eliminate large-departure outliers, defined as trait values greater than three standard deviations from the mean (two values removed for PPI and five for P50). Normalized trait values were used for all analyses, and age at interview, sex, and site of ascertainment were screened as covariates and retained in the analyses when significant ( $p < 0.05$ ). A correction was made for ascertainment bias because the families were recruited through the identification of a proband with schizophrenia and thus are not representative of the general population (46). The significance of the heritability estimate was determined by comparing the full polygenic model with significant covariates included to a sporadic model with the genetic component removed. Each family history subset had the power to detect an additive genetic effect of approximately 0.20 with  $p < 0.05$ . Comparisons of clinical symptom severity and functional status between probands with positive and negative family history were performed in SPSS, version 20 (IBM, Armonk, N.Y.), using analysis of variance adjusted for age, sex, and site as necessary.

## RESULTS

As shown in Table 2, the availability of diagnosis information based on the Family Interview for Genetic Studies allowed for an assessment of the presence or absence of family history of schizophrenia or related disorders (35). Estimates of heritability for PPI and P50 gating were substantially increased in the 97 multiply affected families with a positive family history (47% and 36%, respectively) compared with the entire sample of 296 COGS-1 families (29% and 20%, respectively). By contrast, no evidence for significant heritability was observed for either PPI or P50 gating in the 96 singleton families. For comparison, we evaluated pulse-alone startle magnitude as a measure of initial startle reactivity and observed reasonably consistent heritability estimates between the subsets of families stratified by family history (54% for multiply affected compared with 60% for singleton) and the entire sample (62%). We similarly evaluated P50 S1 amplitude, which, although significantly heritable in all subsets, demonstrated a dramatic increase in heritability in the multiply affected subset (80% compared with 35% and 39% in the singleton subset and in the entire sample, respectively). Conversely, P50 S2 produced reasonably consistent estimates (i.e., within standard error)

**TABLE 1. Description of Interviewed Nuclear Families and FIGS-Extended Families in the COGS-1 Sample<sup>a</sup>**

Family Information	Nuclear Families <sup>b</sup>	Extended Families <sup>c</sup>
Average size	4.6	11.2
Average generations	2.0	2.7
Relative pairs		
Sibling	714	4,113
Half-sibling	17	40
Parent-child	1,530	4,644
Grandparent-grandchild	18	2,368
Avuncular	8	3,294
Cousin	0	235
Subjects		
Total subjects	1,366	3,303
Males / females	736 / 630	1,508 / 1,795
Diagnosis		
Schizophrenia	321	391
Bipolar disorder	25	60
Major depressive disorder	201	296
Other diagnosis	2	53
No psychiatric diagnosis	748	2,449
Unknown	69	49

<sup>a</sup> FIGS=Family Interview for Genetic Studies; COGS=Consortium on the Genetics of Schizophrenia.

<sup>b</sup> Nuclear families include 1,297 subjects directly diagnosed via the Diagnostic Interview for Genetic Studies and 1,337 subjects who provided FIGS information for all included family members and for additional nonparticipating members.

<sup>c</sup> Extended families include 1,952 additional subjects diagnosed via the FIGS information obtained from interviewed participants and best-estimate consensus diagnostic procedures.

between the subsets of families stratified by family history and the entire sample, although it was just below the threshold for significance in the positive family history cohort. Finally, we evaluated the three primary cognitive endophenotypes from COGS-1 (26) and observed consistent heritability estimates (i.e., within standard error) among the subsets of families stratified by family history and the entire sample.

We next compared the schizophrenia probands with positive or negative family history for differences on these gating measures, as well as symptom severity (Table 3). Although differences in PPI and P50 gating deficits were not observed between probands derived from multiply affected versus singleton families, significant clinical differences were observed. Probands with a positive family history had significantly greater clinical severity, as evidenced by lower functioning assessed by the GAF ( $p = 0.011$ ), and had substantially higher global negative symptom scores, as assessed by the SANS ( $p < 0.001$ ). These probands also scored significantly higher across all individual SANS subscales, with particular elevations noted for avolition and anhedonia ( $p < 0.001$ ). Although no significant difference was noted for the global SAPS score, the thought disorder subscale was significantly higher in probands with a positive family history as well ( $p = 0.003$ ). Not surprisingly, these probands also revealed slightly lower levels of education on average than their family history negative counterparts (13.4 versus 14.1 years,  $p = 0.023$ ).

**TABLE 2. Differential Heritability of PPI and P50 Gating Measures in Nuclear Families With Positive or Negative Family History<sup>a</sup>**

Endophenotype	All 296 Families				97 FH+ Families				96 FH– Families			
	N	$h^2_r$	SE	p	N	$h^2_r$	SE	p	N	$h^2_r$	SE	p
PPI	701	0.29	0.09	0.0004	242	0.47	0.13	0.017	215	0.02	0.17	ns
Startle magnitude	821	0.62	0.07	<0.0001	278	0.54	0.11	<0.0001	259	0.60	0.14	<0.0001
P50 gating	568	0.20	0.10	0.019	192	0.36	0.17	0.011	175	0.03	0.17	ns
P50 S1	564	0.39	0.10	<0.0001	190	0.80	0.20	<0.0001	175	0.35	0.20	0.034
P50 S2	564	0.27	0.11	0.005	191	0.19	0.18	ns	174	0.36	0.19	0.026
Continuous performance test	881	0.34	0.06	<0.0001	294	0.31	0.11	0.001	283	0.29	0.12	0.005
Letter-number span	951	0.34	0.06	<0.0001	320	0.31	0.11	0.001	301	0.41	0.13	<0.0001
Verbal learning	949	0.26	0.06	<0.0001	323	0.28	0.12	0.004	299	0.31	0.10	0.001

<sup>a</sup> FH+ families=multiply affected families with a positive history for schizophrenia and/or bipolar disorder; FH– families=singleton families with only the required schizophrenia proband and no evidence of other major psychiatric disorders. Nonsignificant p values (>0.10) are indicated as "ns." For the cognitive measures shown for comparison, "continuous performance test" refers to the Degraded Stimulus version d' measure, "letter-number span" is the reordered condition, and "verbal learning" refers to the California Verbal Learning Test list A total recall score.

**TABLE 3. Comparison of Clinical Symptom Severity and Related Factors Between Probands With Positive or Negative Family History<sup>a</sup>**

Measure	FH+ Probands		FH– Probands		p
	Mean	SE	Mean	SE	
Age at interview (years)	35.7	1.1	34.7	1.1	ns
Education (years)	13.4	0.2	14.1	0.2	0.023
Age at onset	21.2	0.5	21.5	0.6	ns
GAF score	44.4	1.2	49.7	1.7	0.011
PPI	46.3	3.3	42.7	2.9	ns
P50 gating	1.5	0.2	1.1	0.2	ns
SANS total score	10.9	0.6	7.8	0.6	<0.001
Affective flattening	2.3	0.1	1.8	0.2	0.027
Alogia	1.8	0.2	1.2	0.1	0.012
Avolition	2.8	0.2	1.9	0.2	0.000
Anhedonia	2.9	0.2	2.1	0.2	0.001
Attention	1.2	0.1	0.8	0.1	0.092
SAPS total score	6.4	0.4	6.0	0.5	ns
Hallucinations	1.8	0.2	2.0	0.2	ns
Delusions	2.3	0.2	2.2	0.2	ns
Bizarre behavior	0.8	0.1	0.8	0.1	ns
Thought disorder	1.5	0.2	0.9	0.1	0.003

<sup>a</sup> GAF=Global Assessment of Functioning Scale; SANS=Scale for the Assessment of Negative Symptoms; SAPS=Scale for the Assessment of Positive Symptoms; FH+ probands=probands derived from multiply affected families with positive family history; FH– probands=probands derived from singleton families with negative family history. Nonsignificant p values (>0.10) are indicated as "ns."

## DISCUSSION

Substantial heritability of both PPI and P50 gating was observed for multiply affected families with a positive family history. Conversely, neither PPI nor P50 gating displayed any evidence of heritability in the subset of singleton families, in which the probands likely represent sporadic cases of schizophrenia. Pulse-alone startle magnitude showed consistent heritability estimates across all families. While P50 S1 also demonstrated significant heritability across all families, a dramatic increase in S1 heritability was observed for the

positive family history subset. This may suggest that both sensory reactivity and gating are more heritable in schizophrenia families with a positive family history. Alternatively, the heritability of P50 gating in the multiply affected families may be driven, at least in part, by the increased heritability of P50 S1 in this subset, as these two measures are highly correlated ( $r=0.7$ ,  $p<0.001$ ). To our knowledge, this is the first report of differential heritability of PPI and P50 gating in schizophrenia mediated by family history. However, previous studies have suggested the potential impact of positive family history on P50 gating, reporting greater deficits for subjects with both schizotypal personality disorder and a first-degree relative with schizophrenia compared with healthy subjects and those at risk based solely on clinical criteria (12, 13).

Other studies of PPI in both schizophrenia families and healthy twins have shown heritability estimates in the range of 45%–50% (29–31), which are consistent with the heritability estimate of 47% obtained here for the COGS-1 multiply affected families. The heritability of PPI in the entire COGS-1 sample was lower, at 29% (26), which is likely due to the combined influence of the stronger genetic transmission of genes underlying PPI in the multiply affected families and to the apparent lack of genetic transmission in the singleton families on the heritability of this endophenotype. Prior heritability estimates for pulse-alone startle magnitude range from 67% to 70% in schizophrenia families and healthy twins, respectively (29, 30), and show reasonable consistency with the estimates obtained for the entire COGS-1 sample (62%), as well as across the subsets stratified by family history (54%–60%). Taken together, these data suggest that variation in startle magnitude may be generally and highly heritable in humans, and that the inhibition observed in the prepulse paradigm is of particular relevance to schizophrenia, with a substantial genetic component.

P50 gating measured as the difference between the conditioning and test amplitudes has been shown to have robust psychometric properties (e.g., reliability) (47) and a heritability of 41%–46% in healthy twins (32). While the estimated heritability of P50 gating was substantially lower (20%) in

the entire COGS-1 cohort (26), it rose to 36% in the multiply affected families, demonstrating greater consistency with previous estimates derived from healthy subjects. This estimate is also consistent with the estimate of 33% from the Bipolar and Schizophrenia Network on Intermediate Phenotypes (BSNIP) study of schizophrenia and bipolar families (48). Prior assessments of P50 S1 and S2 in healthy twins have revealed heritability estimates of 58%–61% and 52%–56%, respectively (32). Heritability estimates of S1 and S2 in the entire COGS-1 sample were lower, at 39% and 27%, respectively (26), consistent with those observed in BSNIP (43% and 23%, respectively) (48). However, we observed a dramatic increase in the heritability of S1 for the multiply affected subset (80%), while the heritability of this measure in the singleton subset remained consistent with the complete sample (35%). By contrast, the heritability of S2 remained fairly constant between subsets. Some studies have suggested that an increased P50 difference score, which is indicative of poor gating, is related more to a diminished response to the conditioning stimulus (S1) in schizophrenia patients rather than to deficient gating of the response to the test stimulus (S2) (49–51). Collectively, these data suggest that P50 gating is a generally heritable human trait with a substantial genetic component, that individual variability in gating is largely driven by S1, and that both measures specifically detect deficits in schizophrenia patients that appear to segregate with illness in multiply affected families.

The observed heritability for PPI and P50 gating in healthy twins (27–29, 32) may at first seem at odds with the lack of heritability in the singleton families. While the singleton probands themselves would be expected to show deficits, their unaffected relatives would instead reveal a pattern of normal variation in these endophenotypes. Thus, it may be that the deficits in the probands from the singleton families do not aggregate in a consistent manner with the normal variation in their unaffected relatives, which may obscure the heritability of these measures in this subset.

PPI and P50 gating deficits represent schizophrenia-linked biomarkers that can even be identified in subsyndromal populations (10–13). Our results provide further evidence to suggest that gating deficits do in fact represent a core feature of schizophrenia, as PPI and P50 gating deficits were consistent between probands regardless of family history. However, schizophrenia probands differed notably in terms of clinical severity based on family history, with significantly increased negative symptom scores and thought disorder observed for probands with a positive family history. Thus, gating deficits appear to be consistent among schizophrenia patients, regardless of family history, but they co-occur with increased clinical severity in patients with a positive family history.

The primary limitation of this study is that the smaller sample sizes of the subsets of the families stratified by family history reduced power to detect heritability below 20%. While this may have affected the heritability estimates of PPI and P50 gating in the singleton families, there was no

suggestion of heritability for these two endophenotypes at all in this subset. Additionally, PPI and P50 gating are at least partially normalized by the use of atypical antipsychotic medications in schizophrenia patients (7, 9, 52–54). As approximately 85% of all schizophrenia probands were taking atypical antipsychotics at the time of endophenotype testing, this “normalization” effect of atypical antipsychotics complicates the interpretation of heritability data for these endophenotypes in the context of the COGS-1. While the use of atypical antipsychotics may be in part responsible for the lower than expected heritability estimates of PPI and P50 in the complete COGS-1 sample, this effect is independent of family history. The distributions of medication use were comparable between the family history subgroups, with 85% of patients from multiplex families and 87% of patients from singleton families taking atypical antipsychotics at the time of testing. Of the remaining patients, 11% and 10%, respectively, were taking typical antipsychotics, with a minority of subjects not medicated at the time of testing. Thus, the impact of family history on PPI and P50 gating heritability is not confounded by differences in medication use, and neither are the differences in clinical symptom severity that appear to be correlated with family history.

It is noteworthy that the pattern observed here for PPI and P50 sensory registration and gating of substantially higher heritability in the context of increased genetic vulnerability was not seen for the cognitive endophenotypes assessed by COGS-1. This may suggest that the cognitive endophenotypes reflect variation in normal cognitive functioning in the general population in addition to cognitive deficits in schizophrenia, thereby masking the impact of family history. Alternatively, these results may further demonstrate that cognitive endophenotypes are highly polygenic, even in the context of schizophrenia, with many genes contributing small effects to the overall genetic vulnerability (55). Moreover, the portion of the variation in PPI and P50 measures that relates specifically to schizophrenia may be due to greater gene effects observed only in multiply affected families, as was demonstrated in a multigenerational family study of PPI in schizophrenia (31). This latter point is also consistent with the suggestion that cognitive deficits are secondary to primary deficits in early sensory information processing. Overall, these results extend to the genetic realm the work of Callaway and Naghdi (56), who distinguished automatic information processing measures (i.e., PPI, P50 gating) from effortful, controlled processing (i.e., cognition). The neurobiology of automatic responses may be more specific, resulting in a relatively simpler genetic architecture, whereas the controlled processes may be much more complex, with a more widely distributed neural circuit basis and resultantly complex genetic architecture. Indeed, the neural circuit regulation of PPI appears to be relatively constrained within forebrain cortico-striato-pallido-thalamic circuits and their pontine projections (57–59), while the neural circuit regulation contributing to learning and memory is viewed to be more widely distributed across cortical networks. Although these results demonstrate a clear impact of family

history on the heritability of PPI and P50 gating in schizophrenia, more work in this area is needed to identify the causal genes. Furthermore, because all schizophrenia probands demonstrated PPI and P50 gating deficits, regardless of family history, schizophrenia patients of presumably sporadic origin may harbor de novo mutations in the same genes or pathways that underlie the heritability signal for these deficits in multiplex schizophrenia families. Therefore, this familial versus nonfamilial stratification approach to endophenotypes may be useful for resolving the genetic architecture of schizophrenia and may be applicable across many domains of function (60).

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Presented in part at the annual meeting of the American College of Neuropsychopharmacology, Phoenix, Dec. 7–11, 2014.

Supported by NIMH grants R01-MH065571, R01-MH065588, R01-MH065562, R01-MH065707, R01-MH065554, R01-MH065578, R01-MH065558, R01-MH86135, and K01-MH087889.

The authors thank all of the participants and support staff who made this study possible.

Dr. Freedman has a patent through the VA on DNA sequences in *CHRNA7*. Dr. Green has been a consultant to AbbVie, Biogen, DSP, EnVivo/Forum, and Roche; he is on the scientific advisory board of Mnemosyne; and he has received research funds from Amgen. Dr. R.E. Gur has served as a consultant for Otsuka. Dr. Lazzaroni is an inventor on a patent application filed by Stanford University on genetic polymorphisms associated with depression. Dr. Light has served as a consultant for Astellas, Forum, and Neuroverse. Dr. Nuechterlein has received research support from Brain Plasticity, Genentech, and Janssen Scientific Affairs, and has served as a consultant for Brain Plasticity, Genentech, Janssen, and Otsuka. Dr. Swerdlow has served as a consultant for Genco Sciences. The other authors report no financial relationships with commercial interests.

Received May 9, 2015; revision received July 10, 2015; accepted August 10, 2015; published online October 6, 2015.

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