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The Influence of Schizophrenia-Related Neuregulin-1 Polymorphisms on Sensorimotor Gating in Healthy Males

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Background: Neuregulin-1 (*NRG1*) variations have been shown to modulate schizophrenia candidate endophenotypes related to brain structure and function. The objective of this cross-sectional genetic association study was to determine the relationship of six core single-nucleotide polymorphisms within the *NRG1* gene identified as promising schizophrenia risk genes (rs6994992, SNP8NRG221132, SNP8NRG241930, rs3924999, rs2439272 and rs10503929) to prepulse inhibition (PPI) of the acoustic startle reflex, a well validated schizophrenia endophenotype.

Methods: PPI was tested in a highly homogeneous study entry cohort ($n = 445$) of carefully screened healthy, young male army conscripts originating from the Greek LOGOS project (Learning on Genetics of Schizophrenia Spectrum). The QTPHASE from the UNPHASED package was used for the association analysis of each single-nucleotide polymorphisms or haplotype data.

Results: Reduced PPI, particularly at 75-dB_120-msec and 85-dB_60-msec trials, was related to the SNP8NRG241930 G allele and especially the rs6994992 T allele and rs2439272 C allele. Haplotype analysis followed up by risk versus no-risk groups Analysis of variance confirmed that the rs10503929 and rs3924999 SNPs were also associated with PPI reductions, when combined with rs2439272.

Conclusions: We provide solid evidence for a role of *NRG1* risk genotype variations in PPI reductions in a large and demographically and genetically highly homogeneous cohort of healthy young males. These results further validate *NRG1* as a candidate gene for the schizophrenia and spectrum disorders and improve our understanding of its functional mechanisms within the human brain because they suggest an influence of the gene in the neural substrate mediating sensorimotor gating.

Key Words: Endophenotypes, healthy males, LOGOS project, neuregulin-1, prepulse inhibition, schizophrenia

Recent progress in psychiatric genetics has revealed several promising genetic susceptibility factors for schizophrenia, including neuregulin-1 (*NRG1*), a gene located in chromosome 8p12–21. A landmark genetic association study in an isolated Icelandic population originally highlighted an important role for *NRG1* in schizophrenia (1). Since then, there have been several replication attempts, resulting in the usual mixture of positive and negative findings. Some studies have provided supportive evidence of a role of *NRG1* in schizophrenia pathology (2,3), and others have not (4–6).

This inconsistency is in part due to the clinical and genetic heterogeneity of this disorder. One way to overcome this issue is by applying an endophenotypic approach, which involves a quantitative, heritable, trait-related, laboratory-assessed phenotype that is identified in patients and, to a lesser degree, in their unaffected relatives (7). A wide range of schizophrenia endophenotypes including neuropsychological, neurophysiological, structural, and functional brain abnormalities have been evaluated, and their relationship with various candidate genes has been assessed. One of the most promising schizophrenia endophenotypic approaches is the prepulse inhibition (PPI) of the acoustic startle reflex.

PPI is thought to reflect sensorimotor gating, a form of central nervous system inhibition in which irrelevant sensory information is filtered out during the early stages of processing so that attention can be focused on more salient features of the environment (8). Schizophrenia is characterized by deficient PPI and by extension deficient gating, which is thought to result in sensory overload with attentional impairment and subsequent fragmentation of cognitive processes, giving rise to overt symptoms of the disorder (8). PPI in rodents is modulated by activity in a well-defined corticostriatopallido-pontine circuitry (9), which has been confirmed with neuroimaging studies in human subjects (10–12). Consistent with these neuroimaging findings and the notion that sensorimotor gating is important in human cognition (13), neuropsychological studies show that higher PPI levels predict superior executive function (14–16). Deficient PPI is well documented in conditions with frontostriatal pathology and deficient executive function such as schizophrenia (17–19).

A missense mutation on rs3924999 of the *NRG1* gene was found to have a functional effect on PPI in both schizophrenia and healthy control populations (20), although this finding could not be replicated by a more recent study (21). In our study, we examined the possible association of rs3924999 and five additional *NRG1* gene single-nucleotide polymorphisms (SNPs) that have been identified as promising schizophrenia risk genes in the SZGene Database (http://www.schizophreniaforum.org/res/sczgene/default.asp) (22) with PPI in a large sample of healthy male subjects. The data presented here stem from the ongoing LOGOS project (Learning on Genetics of Schizophrenia Spectrum) and originate from the multimodal (gating, cognition, personality) phenotypic assessment and analysis of its first wave of 703 young male Greek army conscripts. Investigating the relation of schizophrenia susceptibility *NRG1* gene variants and variations in PPI levels in the general population would further our understanding of this gene's functional mechanisms within the human brain. An anticipated association of these *NRG1* variants with reduced PPI would provide more evidence for the role of *NRG1* as a schizophrenia candidate gene. Even more

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important, such an association would inform our understanding of the mechanisms through which NRG-1 increases risk for schizophrenia, which was the ultimate goal of the present study.

Methods and Materials

Study Population

The LOGOS project recruited 703 randomly selected young male conscripts from the Greek Army (mean age 22.1 ± 3; range 18–29) during its first phase between June 2008 and July 2009. The study took place between 9 AM and 3 PM in the medical quarters of the Military Training Camp of Candidate, Supply Army officers (SEAP) in Heraklion, Crete. For this purpose, two adjacent rooms in the medical quarters were converted into laboratories. Following public presentation of the study's methods and goals in each consecutive series of new conscripts, all participants willing to volunteer received a detailed information sheet and gave written informed consent before screening. All subjects underwent a review of their medical history and a Mini-International Neuropsychiatric Interview (23) and were tested on a single occasion at some point during their 2 months military training in this establishment. The flowchart in Figure S1 (Supplement 1) shows the inclusion and exclusion criteria and subjects' enrollment. On the basis of these criteria, PPI data were available for 445 subjects of southeast European ancestry confirmed by STRUCTURE analysis using 102 ancestry informative unlinked markers selected for maximal informativeness (24). The study was approved by the Ethics Committee of the University of Crete, the Executive Army Bureau, and the Bureau for the Protection of Personal and Sensitive Data of the Greek State.

Prepulse Inhibition

A commercially available electromyographic startle system (EMG SR-LAB, San Diego Instruments, San Diego, California) was used to examine the eyeblink component of the acoustic startle response. PPI was tested in six trial types of 75- and 85-dB prepulses, at 30-, 60-, and 120-msec prepulse-pulse intervals (six trials per trial type; 36 prepulse-pulse trials in total and 12 pulse-alone trials in a pseudo-random order) according to our standard published protocol (25,26). Stringent criteria ensured high-quality, reliable PPI data, and none of the 445 participants had more than one trial missing per trial type (or two for pulse-alone trials). Equipment setup, procedures, scoring, and trial–subject exclusion criteria are described in detail in Supplement 1 (Startle Measurement).

Genotyping

DNA was extracted by blood or cheek swab samples using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). The following six *NRG1* SNPs were genotyped: rs10503929, rs2439272, rs3924999, rs6994992 (SNP8NRG243177), SNP8NRG221132, SNP8NRG241930; these were chosen because they demonstrate significant or near significant odds ratio in Caucasian studies as per SZGene Database, were missense, or were part of the schizophrenia related haplotype originally reported by Stefansson *et al.* (1). Genotyping was performed blind to phenotype measures by K-Biosciences (Herts, United Kingdom; http://www.kbioscience.co.uk) with a competitive allele-specific polymerase chain reaction system. Genotyping quality control was performed in 10% of the samples by duplicate checking (rate of concordance in duplicates > 99%). Call rate was ~ 99% for all polymorphisms.

Statistical Analysis

Comparison of the genotype groups for each SNP across demographic variables and baseline startle was performed using separate one-way analyses of variance (ANOVAs) or the nonparametric Kruskal–Wallis test as appropriate, based on the deviation from normality. Hardy–Weinberg equilibrium for six markers was checked using Haploview version 4.0 (27). QTPHASE (http://www.mrc-bsu.cam.ac.uk/personal/frank/software/unphased) from the UNPHASED package version 3.1.3 was used for the analysis of genotype associations (28). QTPHASE uses a generalized linear model for quantitative traits, assuming normal distribution of the trait. The trait mean given an individual's genotype data are based on an additive model of haplotypes. Haplotypes with frequencies less than 1% in the whole sample were excluded. *p* values for the trait differences were corrected for multiple testing by running 10,000 permutations of the data. In each permutation, the quantitative scores are randomly reassigned among subjects, and the minimum *p* value is compared with the minimum *p* value over all the analyses in the original data. This allows for multiple testing corrections over all tests performed in a run. Only variants exceeding the .01 level of significance were followed up. For each of those variants, we performed separate mixed-model 3 × 2 × 3 (genotype by prepulse by interval) ANOVAs of % PPI and latency data. Although there were no differences in smoking status (discussed subsequently), the results from all analyses are reported after smoking (cigarettes/day) was taken as a covariate, because smoking is an important moderator of PPI (19,29). Equally, we also included baseline startle as a covariate because of its influence on startle inhibition by a prepulse, which is only partially removed when calculating percent PPI (30). On the basis of our sample size, we were able to detect a small to medium effect size, which for 80% power and α set to 0.05 or 0.01, was Cohen's $d = .027$ or .033, respectively.

Results

Table 1 summarizes the genotype distribution and minor allele frequency of the *NRG1* polymorphisms in our sample. Genotype frequencies were distributed in accordance with Hardy–Weinberg equilibrium. Our polymorphisms were localized in two regions of the *NRG1* gene. The rs6994992, SNP8NRG221132, and SNP8NRG241930 polymorphisms, which were in strong linkage disequilibrium (LD), are localized in the 5′ upstream region of the *NRG1* gene. The rs3924999, rs2439272, and rs10503929 variants were in weak LD and are localized in a region more proximal to the 3′ end of the gene (Table S1 in Supplement 1). There were no differences in demo-

Table 1. Genotype, Allele, and Minor Allele Frequencies of the *NRG1* Polymorphisms

Marker[a]	Genotype			Minor Allele Frequency	Hardy–Weinberg Equilibrium *p* Value[b]
rs6994992 (99.3%)	C/C	C/T	T/T	.41	.87
	153	212	77		
SNP8NRG221132	G/G	G/A	A/A	.19	.36
(100%)	297	129	19		
SNP8NRG241930	G/G	G/T	T/T	.34	.77
(98.7%)	192	194	53		
rs3924999 (99.3%)	C/C	C/T	T/T	.37	.74
	175	203	64		
rs2439272 (99.1%)	C/C	C/T	T/T	.38	.17
	178	193	70		
rs10503929 (100%)	T/T	T/C	C/C	.17	.23
	310	118	17		

[a]The percentage refers to call rate for each polymorphism.
[b]The allele distributions are consistent with Hardy-Weinberg expectations.

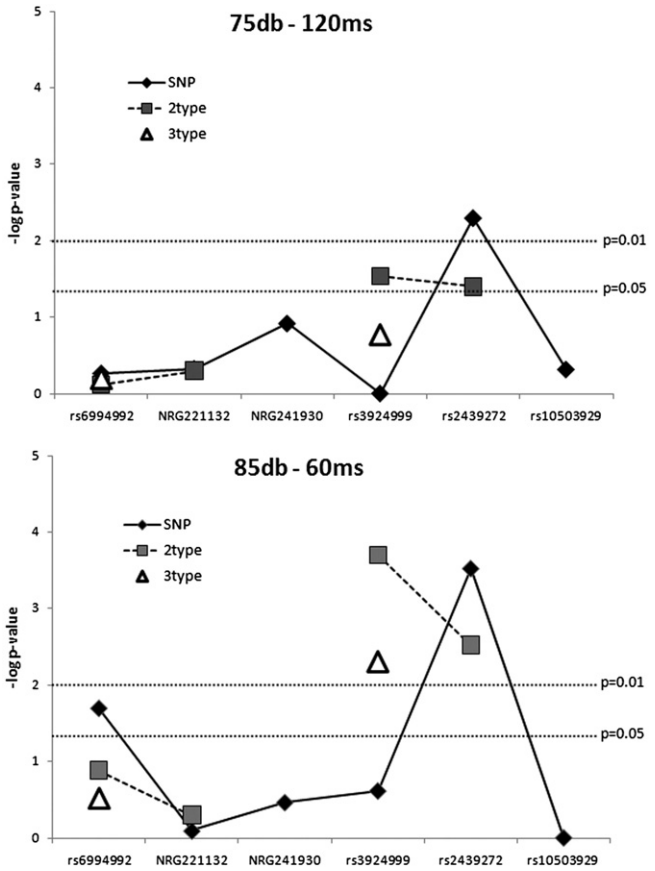

Figure 1. Summary of results for allelic (single-nucleotide polymorphisms [SNP]) and haplotypic [two (2type) and three (3type) marker sliding window] analyses between the SNPs and 75 db_120 msec (top) and 85 db_60 msec (bottom) trial types. The rs2439272 shows allelic association in both prepulse inhibition trials. The diplotypes rs3924999-rs2439272 and rs2439272-rs10503929 were significant at $p < .05$ and $p < .01$ for 75 db-120 msec and 85 db-60 msec stimuli, respectively. The rs3924999-rs2439272-rs10503929 triplotype showed a significant association with 85 db - 60 msec at $p < .01$. The rs6994992 polymorphism was significant for 85 db-60 msec at $p < .05$. Two thresholds are indicated with dashed horizontal lines, starting from the top down: $p = .01$ and $p = .05$. p values are corrected by running 10,000 permutations.

graphic variables between the *NRG1* genotypes for each SNP (Table S2 in Supplement 1).

Single-Marker Association Analysis

Figure 1 and Table 2 show the p values of the association of *NRG1* SNPs with baseline startle and PPI as revealed by the QTPHASE after correction with permutation test. The T allele of the rs3924999 was associated with reduced baseline startle (mean ± SD, TT: 122.9 ± 73.2; TC: 136.5 ± 86.2; CC: 151.3 ± 90.6; Cohen's d [TT vs. CC]: .33). A pattern of association can be seen whereby the T, G, and C alleles of the rs6994992, SNP8NRG241930, and rs2439272 variants respectively, were associated with lower PPI levels. The rs6994992 and rs2439272 polymorphisms were significant at $p <$ .01 in at least one trial type (Figure S2 in Supplement 1). A mixed-model ANOVA of PPI with genotype as the grouping factor (three levels) and prepulse and interval as the within-subject factors revealed significant genotype main effects (rs6994992: $F(2,437) = 3.97$, $p = .02$, partial $\eta^2 = .018$ and rs2439272: $F(2,436) = 6.32$, $p = .002$, partial $\eta^2 = .028$). We repeated the UNPHASED analysis and the follow up ANOVAs described earlier, taking baseline startle and/or smoking and/or IQ as the covariates; following this procedure, the results did not change or the p values slightly improved.

Haplotype Analysis

For the haplotype analysis, we performed sliding window association tests, using two- and three-marker combinations for the two *NRG1* regions (5′ upstream region: rs6994992, SNP8NRG221132, and SNP8NRG241930; 3′ end region: rs3924999, rs2439272, and rs10503929; Figure 1, Table 2). No haplotypes were significantly associated with baseline startle. Overall, we found that the diplotypes rs3924999-T-rs2439272-C and rs2439272-C-rs10503929-T and the triplotype rs3924999-T-rs2439272-C-rs10503929-T were associated with PPI at $p < .01$ in at least one trial type, whereas the diplotype rs6994992-T-SNP8NRG221132-G showed significant association only at $p < .05$. We then followed up the rs3924999-rs2439272 and rs2439272-rs10503929 diplotypes, which were significant at $p < .01$. For each diplotype, we divided our population into a risk group, if individuals were homozygous for both risk SNPs or homozygous for one SNP and heterozygous for the other, and into a no-risk group if they were homozygous for any of the no-risk SNP. We excluded subjects that were heterozygous for both polymorphisms (Table S3 in Supplement 1). Following this grouping, we performed a mixed-model ANOVA of PPI with diplotype as the grouping factor (risk, no risk) and prepulse and interval as the within-subject factors revealed significant main effects of genotype [rs2439272-rs10503929: $F(1,387) = 8.82$, $p = .003$, partial $\eta^2 = .022$; rs3924999-rs2439272: $F(1,334) = 8.12$, $p = .005$, partial $\eta^2 = .024$; Figure 2]. There were no differences in demographic variables between the *NRG1* diplotypic groups (Table S4 in Supplement 1). When our data were reanalyzed with the UNPHASED taking baseline startle and/or smoking and/or IQ as covariates, the results did not change or the p values slightly improved.

Discussion

To the best of our knowledge, this is the first study to examine the effect of multiple-risk *NRG1* genetic variants implicated in the etiopathogenesis of schizophrenia on PPI. We provide solid evidence that three SNPs, the SNP8NRG241930 G allele, and especially the rs6994992 T and rs2439272 C alleles, were associated with reduced PPI. In addition, two more SNPs (rs10503929 and rs3924999) were also associated with PPI reductions when combined with rs2439272.

Meta-analyses in SZGene database do not yet fully support the C allele of the rs2439272 polymorphism as a strong risk factor in schizophrenia (odds ratio [OR] T vs. C allele: .79; 95% confidence interval [CI]: .6–1.05), although for Caucasians, this OR is based on only three studies (2,6,31). Our findings strongly suggest that this allele is an important determinant of PPI in healthy subjects. Given the increasing prominence of PPI as a strong schizophrenia endophenotype, our study encourages further exploration of this SNP in the pathophysiology of schizophrenia. In addition, the C (risk) allele of this polymorphism was part of two diplotypes along with the T alleles of the rs10503929 and rs3924999 variants. Interestingly, the T allele of the rs10503929 polymorphism is the only *NRG1* variant found to be associated significantly with schizophrenia in the SZGene database (OR C vs. T allele: .88; 95% CI: .81–.96). This is a functional polymorphism exchanging methionine (T allele) to threonine (C allele). The rs3924999 is another functional polymorphism, which exchanges arginine (C allele) to glutamine (T allele). The functional effects of these amino acid exchanges for both missense polymorphisms are unknown.

Our findings indicate that these *NRG1* polymorphisms act on brain areas that modulate PPI, an endophenotype implicated in schizophre-

Table 2. Adjusted *p* Values from Permutation Test for Association of Startle and PPI for *NRG1* SNPs and Haplotypes

	Polymorphisms	Baseline Startle	Prepulse Inhibition (PPI) 75–30	PPI 75–60	PPI 75–120	PPI 85–30	PPI 85–60	PPI 85–120
SNPs	rs6994992	>.2	***.048*, *(t) (−.006)***	>.5	>.5	**.01**, **T: (−.006)**	***.02*, *T: (−.006)***	>.1
	SNP8NRG221132	>.8	.09	>.9	>.4	>.7	>.8	>.3
	SNP8NRG241930	>.8	***.04*, *G: (−.006)***	>.5	>.1	***.02*, *G: (−.006)***	>.3	>.9
	rs3924999	.009 **T: (−.002)**	>.3	>.6	>.9	>.8	>.2	>.4
	rs2439272	>.6	***.04*, *C: (−.006)***	.09	**.005**, **C: (−.009)**	***.047, C: (−.005)***	**.0003**, **C: (−.01)**	***.047, C: (−.005)***
	rs10503929	>.4	>.6	>.8	>.4	>.8	>.9	>.7
Diplotypes	rs6994992	>.1	***.037, C-A: .01 [.009]***	>.9	>.7	>.1	>.1	>.3
	SNP8NRG221132							
	SNP8NRG221132	>.3	>.1	>.6	>.5	>.1	>.5	>.6
	SNP8NRG241930							
	rs3924999	>.1	.076	>.3	.028	>.2	.00028	.07
	rs2439272				***C-T: .02 [.01]***		**T-C: .005 [−.004]**	
							C-T: .0001 [.016]	
	rs2439272	>.6	>.1	.06	.04	.047	.004	>.2
	rs10503929				***C-T: .04 (ref)***	***T-C: .047 [.019]***	**C-T: .005 (ref)**	
					T-T: .005 [.01]		**T-T: .0027 [.01]**	
Triplotypes	rs6994992	>.1	>.2	>.9	>.6	>.4	>.3	>.5
	SNP8NRG221132							
	SNP8NRG241930							
	rs3924999	>.5	>.1	.1	>.1	.085	.005	>.3
	rs2439272						**C-T-T: .0005 [.016]**	
	rs10503929						**T-C-T: .017 [−.004]**	

PPI, prepulse inhibition; *NRG1*, neuregulin-1; SNP, single-nucleotide polymorphisms.

Numbers represent the overall *p* value for each SNP or diplotype. In the case of diplotypes, when UNPHASED revealed an overall *p* value <.05, then *p* values for specific haplotypes are presented. Numbers in brackets represent the estimated additive genetic value between the specific variant and all the others pooled together, and plus or minus signs indicate increases or reductions in PPI respectively. *p* values < .05 are in bold and italicized; *p* values <.01 are in bold.

nia pathology and dopaminergic dysfunction (8,19,32). *NRG1* and its receptor (ErbB4) have been identified as susceptibility genes for schizophrenia (1,33). Changes in the expression levels of *NRG1* splicing isoforms and ErbB4 protein are also found in postmortem brains and peripheral blood cells of schizophrenia patients (2,34–36) although the pathophysiologic contribution of abnormal NRG1/ErbB4 signaling to schizophrenia is largely unresolved. Neuregulin-1 is one of the neurodevelopmental regulators that are involved in neuronal migration, axon pathway finding, myelination, and synaptogenesis (37–40). Thus, abnormalities in its expression can be implicated in the neurodevelopmental hypothesis of schizophrenia, and indeed, upregulation of Type-1 *NRG1* expression is reported in schizophrenia brain pathology (35–37), whereas transgenic mice overexpressing Type 1 *NRG1* (41) or peripheral administration of Type-1 *NRG1* protein in mouse pups, both lead to PPI deficits and other schizophrenia-like behavioral impairments (42). The latter is through activation of midbrain ErbB4, the receptor for *NRG1*, which is expressed exclusively by the midbrain dopamine neurons (43). Activation of ErbB4 leads to elevation of the expression, phosphorylation, and enzyme activity of tyrosine hydroxylase, ultimately inducing a hyperdopaminergic state characterized by deficient PPI reversible by risperidone (42). In rodents, PPI is modulated by activity in a well-defined corticostriato-pallido-pontine circuitry (9), which has been confirmed with neuroimaging studies in human subjects (10–12). It is conceivable that the rs3924999, rs2439272, and rs10503929 variants, which are contained within Type I isoform of *NRG1*, might lead to alterations of the transcription levels or activity of Type-1 *NRG1* leading to reduced PPI through an ErbB4/dopaminergic mechanism (or both).

Recent studies found a significant effect of the T allele of the rs3924999 polymorphism on PPI (20) and in an antisaccade task (44). We present first evidence that this allele significantly reduced baseline startle, a finding that requires replication. However, in agreement with a recent study (21), we failed to replicate the PPI reduction observed previously in association with this allele (20). By contrast, we provide evidence that this (rs3924999) as well as the rs10503929 functional polymorphisms are determinants of sensorimotor gating in healthy human subjects when combined with the risk C allele of the rs2439272. It is notable that the haplotypic variants associated with reduced PPI contain the risk alleles previously associated either with schizophrenia or PPI reductions. It is also worth mentioning that meta-analysis in SZGene database does not provide evidence for association of the rs3924999 polymorphism with schizophrenia (OR T vs. C allele: .99; 95% CI: .9, 1.08). Because positive studies on the effects of this SNP on various endophenotypes from different laboratories are beginning to emerge (20,44), it is perhaps legitimate to speculate that the negative findings in schizophrenia database may be due to the diverse phenotype as defined by the diagnosis.

We also found that the G allele of the SNP8NRG241930 polymorphism was associated with reduced PPI. This polymorphism is part of the core "at-risk" haplotype (HAP_{ICE}), consisting of five SNPs, including the SNP8NRG221132 and rs6994992 (SNP8NRG243177), and two microsatellite markers spanning about 300 kb of the first exon of *NRG1* and the upstream sequences originally reported in Icelandic families (1). According to a meta-analysis as described in SZGene database, the G allele of the SNP8NRG241930 polymorphism might be a risk factor for schizophrenia in Caucasians (OR T vs. G allele: .95; 95% CI: .89, 1.01). Moreover, the G allele of this polymorphism, combined with the G and T alleles of the SNP8NRG221132 and rs6994992 SNPs, respectively, is part of a haplotype that predicts higher levels of Type IV messenger RNA expression (36). One possible mechanism through which the SNP8NRG241930 variant leads to reduced PPI could be the upregulation of the Type IV *NRG1*. A mouse model with targeted transgenic alteration of the Type IV *NRG1* may be needed to provide precise understanding between the genotype–phenotype relations in mice and in humans.

Finally, we provide evidence that another SNP of the HAP_{ICE}—namely, the T allele of the rs6994992 polymorphism is associated with reduced sensorimotor gating. This polymorphism has been shown to be functional with the risk T allele associated with higher levels of Type IV messenger RNA expression (36). Additionally, the T allele of this SNP has been correlated with attenuated frontal and temporal activation during performance of the Hayling sentence completion task and decreased premorbid IQ in a group of young individuals at high risk for developing schizophrenia (45), decreased performance in a spatial working memory task (n-back) (46), decreased white matter density and connectivity in the anterior limb of the internal capsule in healthy subjects (47), increased lateral ventricular volume in patients with schizophrenia experiencing their first psychotic episode (48), and deficit in global smooth eye pursuit performance (49). Our results provide further evidence for the importance of this variant in the pathogenesis of schizophrenia. It is important to note at this point that the *NRG1*-PPI association found in this study may have implications for bipolar disorder where PPI deficits (50–52) and associations with *NRG1* (53–55) have also been identified. Also, it should be borne in mind that PPI deficits are seen in other neuropsychiatric populations with frontostriatal pathology (e.g., Tourette's syndrome, obsessive-com-

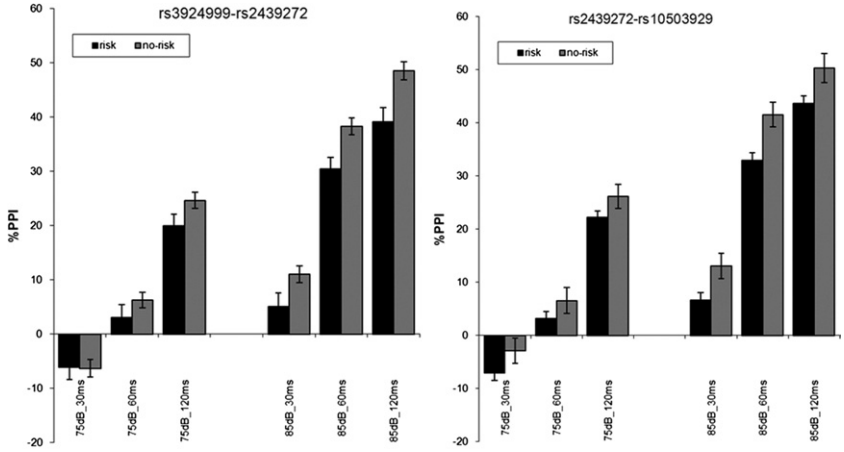

Figure 2. Percent prepulse inhibition (% PPI) for the risk and no-risk groups of the rs3924999-rs2439272 (left) and rs2439272-rs10503929 (right) diplotypic groups. Bars represent SEM. $*p < .05$, $**p < .01$.

pulsive disorder, Huntington's disease, autism) (56), and therefore future research should determine whether our findings may have broader implications than for schizophrenia alone.

The trial 85-dB_60 msec was the most frequently associated trial with *NRG1* variants. This observation is particularly interesting in light of previous results showing stability of PPI deficits at 60-msec interval in schizophrenia patients, especially those with the greatest functional impairment (19), suggesting that sensorimotor gating at this interval may be the most sensitive to genetic influences relevant to the biology of schizophrenia. Perhaps it is relevant here that reflex inhibition at this prepulse–pulse interval is regulated by processes standing at the border between automatic or unconscious preattentive and attentional inhibition, which can be subject to conscious volitional manipulation (57). The conceptual implication of reduced PPI is that information conveyed by a stimulus (i.e., prepulse) may be at greater risk to be corrupted and therefore to overload with noise or not to enter a hierarchical process that would lead to its appropriate cognitive, sensory, or motor/behavioral consequence (58–60). Extrapolating from the foregoing, it is possible that one (of many) theoretical pathophysiologic routes to *NRG1*-associated psychotic experience, may be *NRG1*-related inhibitory deficits at the transitional zone between consciously accessible and unconscious processing, which is of particular importance for regulating the contents of consciousness (61–63), thus allowing predominance of unconscious material.

Sensorimotor-gating deficits as assessed by PPI are observed in disorders of frontostriatal pathology (56); however, the most consistent findings are PPI deficits in schizophrenia patients (17–19,64–65), their first-degree relatives (66,67), and individuals with schizophrenia spectrum disorder, such as schizotypal personality disorder (68) and during the prodromal stage (69). Twin (70) and family (71,72) studies demonstrate that PPI heritability is approximately 50%. In recent years, there has been an increasing number of association studies in healthy humans and schizophrenia patients suggesting that genetic variations of the serotonin-2A receptor (*5-HT$_{2A}$R*) (73), catechol-*O*-methyltransferase (*COMT*) (25,74–76), dopamine-D3 receptor (*DRD3*) (26), *NRG1* (20), proline dehydrogenase (*PRODH*) (77), and α3 subunit of the nicotinic acetylcholine receptor (*CHRNA3*) (78) may all affect PPI. Interestingly, PPI showed a simple mode of transmission that is useful for successful application in molecular genetic research, while other endophenotypes such as verbal fluency and spatial working memory demonstrated a polygenic, multifactorial model (72), suggesting that PPI can be a superior endophenotype for identification of genetic variants in schizophrenia spectrum disorders. Conclusively, PPI has emerged as an important and validated endophenotypic marker, cross-fertilizing genetic studies of schizophrenia. Future studies are expected to be fruitful, highlighting novel genetic polymorphisms as well as epistatic effects that will explain a larger fraction of PPI variance.

The LOGOS cohort provides a comprehensive endophenotypic assessment of schizophrenia related intermediate phenotypes in a demographically and genetically homogeneous population consisted from healthy, young, Greek men. This sample homogeneity coupled with an endophenotype with high precision of phenotypic definition, that is, the specific response measure of PPI (79), which might reflect gene effects more directly than broader constructs such as neurocognitive deficits (72), increase multiplicatively the power of this cohort to detect genetic variants, thus obviating Type I and II errors (7). The high reliability of recording PPI (80–83) and the stringent scoring criteria applied in this cohort, secure the high-quality data required for endophenotypic studies aiming to detect gene effects. Importantly, the healthy male volunteer model of studying functional mechanisms of genes is devoid of confounds that strongly affect the study and interpretation of PPI deficits in patient populations, such as gender and medication (19,84), presence of symptoms (8,85), and the brain effects of psychiatric illness episodes. Last but not least, automatic sensorimotor gating as measured by the uninstructed PPI paradigm, is uniquely independent of subjects' motivation, engagement, and social desirability biases. All of these factors taken together increase confidence in the conclusions reached, about the functional mechanisms of the *NRG1* gene. Nevertheless, our results need to be replicated in an independent cohort, although it remains to be seen whether they hold across genders and over a wider age range. However, our sample is representative of the Greek population as far as genetic variation is concerned.

In conclusion, we provide solid evidence for a role of risk *NRG1* genotype variations in PPI deficiencies in a large and demographically and genetically highly homogeneous cohort of young, healthy male subjects. This finding suggests an influence of the gene in the neural substrate mediating sensorimotor gating and further validates *NRG1* as a candidate gene for the schizophrenia and spectrum disorders.

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