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ORIGINAL PAPER

# Neuregulin-1 genotypes and eye movements in schizophrenia

**H. Magnus Haraldsson · Ulrich Ettinger · Brynja B. Magnusdottir · Andres Ingason · Samuel B. Hutton · Thordur Sigmundsson · Engilbert Sigurdsson · Hannes Petursson**

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**Abstract** Neuregulin-1 (NRG-1) is a putative susceptibility gene for schizophrenia but the neurocognitive processes that may involve NRG-1 in schizophrenia are unknown. Deficits in antisaccade (AS) and smooth pursuit eye movements (SPEM) are promising endophenotypes, which may be associated with brain dysfunctions underlying the pathophysiology of schizophrenia. The aim of this study was to investigate the associations of NRG-1 genotypes with AS and SPEM in schizophrenia patients and healthy controls. Patients ($N = 113$) and controls ($N = 106$) were genotyped for two NRG-1 single nucleotide polymorphisms (SNPs); SNP8NRG222662, a surrogate marker for the originally described Icelandic NRG-1 risk haplotype, and SNP8NRG243177, which has recently been associated with individual differences in brain function. Subjects underwent infrared oculographic assessment of AS and SPEM. The study replicates previous findings of impaired AS and SPEM performance in schizophrenia patients (all $P < 0.005$; all $d = 0.5$–$1.5$). SNP8NRG243177 risk allele carriers had marginally increased variability of AS spatial error ($P = 0.050, d = 0.3$), but there were no significant genotype effects on other eye movement variables and no significant diagnosis-by-genotype interactions. Generally, risk allele carriers (G allele for SNP8NRG222662 and T allele for SNP8NRG243177) had numerically worse performance than non-carriers on most AS and SPEM variables. The results do not suggest that NRG-1 genotype significantly affects AS and SPEM task performance. However, the power of the sample to identify small effects is limited and the possibility of a type II error must be kept in mind. Larger samples may be needed to reliably investigate such gene effects on oculomotor endophenotypes.

**Keywords** Schizophrenia · Neuregulin-1 · Antisaccade · Smooth pursuit · Endophenotype

## Introduction

There is strong evidence from behavioral genetic studies for involvement of genetic factors in the etiology of schizophrenia [50]. Although no genes of major effect on schizophrenia liability are likely to be found, several putative susceptibility genes for the disorder have been described; see [44] for references, such as neuregulin-1 (NRG-1), dystrobrevin binding protein-1 (DTNBP1) and disrupted in schizophrenia-1 (DISC-1). Evidence is also cumulating that epigenetic phenomena such as DNA methylation changes [41] and copy number variations [56] may increase risk for schizophrenia.

Association of a NRG-1 haplotype with schizophrenia was first reported in an Icelandic sample [58] and subsequently replicated in a Scottish sample [57]. These findings were followed by studies in several ethnic populations that

H. M. Haraldsson (✉) · B. B. Magnusdottir · T. Sigmundsson · E. Sigurdsson · H. Petursson
Division of Psychiatry, Landspitali University Hospital, Hringbraut, 101 Reykjavik, Iceland
e-mail: hmagnus@landspitali.is

U. Ettinger
Department of Psychiatry, Ludwig-Maximilians-University, 80336 Munich, Germany

A. Ingason
Institute of Biological Psychiatry, Mental Health Center Sct. Hans, Copenhagen University, 2 Boserupvej, Roskilde 4000, Denmark

S. B. Hutton
Department of Psychology, Sussex University, Brighton BN1 9QH, UK

all reported associations between schizophrenia and genetic markers either within the original core haplotype or related markers [8, 13, 14, 18, 33, 36, 43, 59, 64, 66, 67]. However, several negative findings have also been reported [9, 28, 29, 45, 61] and the mechanisms by which NRG-1 variants may contribute to the pathogenesis of schizophrenia have not been identified. Therefore, the relationship between NRG-1 and schizophrenia is not conclusive.

The variable and obscure clinical presentation of schizophrenia complicates studies of how genetic factors are involved in the disorder. This problem may possibly be circumvented by employing endophenotypes. Endophenotypes have been defined as biological or behavioral features, which may be more closely related to underlying disease genes than the complex clinical phenotype [4, 16]. Deficits in antisaccade (AS) and smooth pursuit eye movements (SPEM) are promising endophenotypes for genetic studies of schizophrenia [6]. The validity of AS and SPEM as endophenotypes in schizophrenia is supported by evidence that unaffected relatives of schizophrenia patients have worse performance than subjects without family history of the illness [7, 27], twin studies have found significant heritability of AS and SPEM performance [30, 37] and high temporal stability of task performance has been reported in patients, relatives and controls [5, 12].

Although the genetic factors underlying AS and SPEM deficits are still not fully known several studies have been published in the last decade linking markers on chromosome 6p [1, 2, 39], chromosome 22q [42] and polymorphisms in the catechol-*O*-methyl transferase (COMT) [21, 40, 48, 60], dopamine D3 receptor [47], phospholipase A2 [46], regulator of G-protein signaling 4 (RGS4) [53] and dopamine transporter (DAT1) [65] genes with eye movement impairments.

In this study, we investigated two NRG-1 markers; the SNP8NRG222662, which has been found to be a particularly good surrogate marker for the original Icelandic risk haplotype ($r^2 = 1$) (deCODE Genetics, unpublished data) and SNP8NRG243177 (rs6994992), which is part of the original haplotype [58] and has on its own shown strong association with schizophrenia [57]. In SNP8NRG222662, the G allele tags the core risk haplotype and in SNP8NRG243177 the T allele is risk associated.

The aim of the present study was to investigate the association between AS and SPEM performance and variants in the NRG-1 gene. We studied schizophrenia patients and healthy controls as it has been shown that some gene–endophenotype associations may depend on disease status [60, 65]. The study was carried out in the Icelandic population, which due to its relative genetic homogeneity presents an ideal platform for the investigation of human genetics [17]. This is to our knowledge the first study investigating possible associations between NRG-1 risk genotypes and eye movement endophenotypes. We hypothesized that carriers of risk alleles in SNP8NRG222662 and SNP8NRG243177 (rs6994992) would perform worse on the AS and SPEM tasks than non-carriers.

The AS and SPEM data presented here were published earlier along with prosaccade and visual fixation data and analyses of several psychometric properties of these eye movement tasks [23].

## Method

### Participants

Participants were selected from a large group of participants in a previous study for which they provided blood samples for DNA analysis [58]. From this group a list of potential participants was created by deCODE Genetics based on the carrier status of the SNP8NRG222662 risk G allele. Both patient and control groups were enriched with risk allele carriers aiming toward having at least 30% risk carriers in each group. This was done in order to increase the power of the carrier versus non-carrier comparison of eye movement task performance as the estimated frequency of the risk haplotype is only 15.4% in patients and 7.5% in the general population [58]. The study design therefore does not permit a test of the association between NRG-1 SNPs and schizophrenia.

The sample included 113 schizophrenia patients (mean age 41 (SD = 10), 73% males) and 106 healthy controls (mean age 41 (SD = 10), 65% males). Patients were recruited from the Division of Psychiatry at the Landspitali-University Hospital in Reykjavik. The diagnosis of schizophrenia was confirmed by an experienced psychiatrist, who was blind to genotype status, according to Research Diagnostic Criteria (RDC) [52] using the Schedule of Affective Disorders and Schizophrenia—Lifetime Version (SADS-L) [51]. Patients' symptom levels were assessed using the Positive and Negative Syndrome Scale (PANSS) [31]. Over 90% of patients were on stable (>6 months) antipsychotic treatment.

Healthy controls were recruited from the local community and were screened for history of axis I psychiatric disorder using the Mini-International Neuropsychiatric Interview (M.I.N.I.) [49]. Subjects who had first or second-degree relatives with psychotic illnesses were excluded. Subjects with history of neurological illness (e.g. seizures, stroke, Parkinson's disease), neuro-opthalmological deficits, head trauma (causing loss of consciousness) and substance abuse/dependence in the past 12 months were excluded. All participants were Icelandic, between 18 and 55 years old and provided written, informed consent. The

study protocol was approved by the Icelandic Scientific Ethics Committee.

### Eye movements

Eye movements were recorded from the left eye using infrared oculography (IRIS 6500; Skalar Medical BV, Delft, The Netherlands) sampled at 500 Hz. The examiners were not aware of the subjects' genotype status. A white circular target (0.3°) was presented on a black background. Each task was preceded by a 3-point calibration (0°, ±12°). For SPEM, a triangular target waveform was employed at 12°, 24° and 36°/s, respectively. The AS and SPEM tasks are described in detail in a previous publication [23].

For AS eye movement analysis Eyemap 2.1 (AMTech GmbH, Weinheim, Germany) was used and SPEM analysis was carried out using custom software written in LabView. All eye movement data were scored blind to group and genotype status by one rater (HMH) and confirmed by a second rater (UE). Inter- and intra-rater reliabilities were high ($r = 0.93$–$0.99$).

For ASs, the following dependent variables were employed. *Reflexive error rate* on the AS task reflects the percentage of error trials over the total number of valid trials. *Latency* of correct AS was defined as the time (ms) from target appearance to saccade initiation. *Amplitude gain* was calculated as the primary saccade amplitude divided by target amplitude multiplied by 100. *Spatial error* was calculated as follows. First, for each trial, the difference between primary saccade amplitude and target amplitude was calculated and the result was divided by the target amplitude. This measure gives the residual error. Second, the residual error scores were then averaged across all saccades and multiplied by 100. This measure gives each participant's percentage of spatial error. A perfectly accurate saccade thus attracts a spatial error score of 0%; higher scores denote greater spatial error.

For all AS variables (reflexive error rate, latency, amplitude gain and spatial error), the mean score across trials was given for each participant. Additionally, for latency, gain and spatial error each participant's individual standard deviation was calculated. The individual standard deviation is a measure of variability.

For SPEM, the following dependent variables were employed. Steady-state smooth pursuit *velocity gain* was calculated by dividing mean eye velocity by target velocity. This was only done for segments of pursuit occurring in the central 50% of each ramp, excluding eye blinks and saccades. These values were time-weighted and subsequently averaged. Saccades that occurred during SPEM were automatically identified on the basis of minimum amplitude (1°) and velocity (30°/s) criteria, and were excluded from the analysis of pursuit gain. The number of saccades was established at each target velocity and divided by the duration of the task in order to yield measures of *saccadic frequency* (N/s).

### Genotyping

DNA was isolated from whole blood or lymphoblastoid cell lines using an extraction column method (Qiagen Inc, Valencia, CA, USA). Genotyping of SNP8NRG222662 and SNP8NRG243177 (rs6994992) was carried out using the Centaurus platform (Nanogen Inc. San Diego, CA, USA).

### Statistical analysis

Statistical analysis was carried out using the Statistical Package for the Social Sciences (SPSS) version 11 (SPSS Inc. Chicago, IL). Level of significance was set to $P < 0.05$. Outliers in the eye movement data were identified using box plots and all extreme values (more than 3 box-lengths from edge of box) were removed. Distributions of eye movement variables were assessed for normality using the skewness index. If positively (>1) or negatively (<1) skewed, variables were transformed using square root or square transformations, respectively.

Because of the small number of SNP8NRG222662 G and SNP8NRG243177 T risk allele homozygotes, the risk allele hetero- and homozygotes were combined (G/G + G/A and T/T + T/C) for all statistical analyses. Effects of diagnosis (patient, control) and genotype (G, non-G for SNP8NRG222662 and T, non-T for SNP8NRG243177) on AS performance and diagnosis-by-genotype interactions were analyzed using separate 2-by-2 between-groups analyses of variance (ANOVA). Smooth pursuit data were analyzed using repeated measures ANOVA with velocity (12°, 24°, 36°/s) as within subjects factor and diagnosis (patient, control) and genotypes (G, non-G and T, non-T) as between subjects factors in separate ANOVAs for each genotype.

Chi-square test was used to analyze the associations between NRG-1 genotypes and gender. The relationships between genotypes and age, age of illness onset and PANSS scores were investigated using one-way ANOVA.

## Results

### Genotype, demographic and clinical data

Eye movement and SNP8NRG222662 genotype data were obtained from all 113 schizophrenia patients and 106 controls. Due to assay problems, 1 patient and 4 controls could not be genotyped for SNP8NRG243177. Forty-two

percent of patients and 39% of controls were carriers of the SNP8NRG222662 G risk allele.

There were no significant associations of gender with allele status in the patient group, control group and the combined sample (all $P > 0.17$). There was no significant age difference between SNP8NRG222662 G carriers and non-G carriers in patients, controls or the combined sample (all $P > 0.20$). However, for SNP8NRG243177, there was a significant age difference between T carriers and non-T carriers in the patient group ($P = 0.036$) but not in the control group ($P = 0.66$). Patient T carriers were significantly older than the non-T carriers. In the combined sample, the T carriers fell just short of being older than the non-T carriers ($P = 0.06$). Therefore, all analyses of SNP8NRG243177 Genotype effects on eye movements were performed with age as a covariate.

Neither genotype was associated with the patients' age of illness onset (both $P > 0.30$), total PANSS score (both $P > 0.25$) or the individual PANSS sub-scores (all $P > 0.18$). Demographic and clinical statistics by diagnosis and genotype are summarized in Table 1.

## Antisaccades

Data from seven patients and three controls could not be analyzed due to poor quality related to difficulties the participants had in performing the task. Descriptive AS statistics are demonstrated in Table 2. As previously described [23], the patients had significantly more reflexive errors, longer and more variable latency and smaller amplitude gain than controls (all $P < 0.005$, all $d > 0.5$).

### *SNP8NRG222662*

There were no significant main effects of the SNP8NRG222662 genotype on AS reflexive error rate ($F[1,208] = 1.3$; $P = 0.25$), latency ($F[1,207] = 1.3$; $P = 0.29$), amplitude gain ($F[1,206] = 0.6$; $P = 0.60$), spatial error ($F[1,205] = 1.1$; $P = 0.30$) or the variability of latency ($F[1,204] = 0.8$; $P = 0.37$) and amplitude gain ($F[1,206] = 1.1$; $P = 0.29$). There was a trend toward a difference in the variability of spatial error ($F[1,203] = 3.4$; $P = 0.068$; $d = 0.26$), suggesting greater variability in G allele carriers than non-carriers. There were no significant diagnosis-by-genotype interactions (all $P > 0.15$). However, for all AS variables, except amplitude gain and latency variability, carriers of the risk allele had numerically (4–10%) worse performance.

### *SNP8NRG243177*

There were no main effects of SNP8NRG243177 genotype on AS error rate ($F[1,203] = 1.7$; $P = 0.19$), latency ($F[1,202] = 0.03$; $P = 0.85$), or amplitude gain ($F[1,201] = 0.01$; $P = 0.91$). For spatial error there was a trend ($F[1,201] = 2.9$; $P = 0.09$; $d = 0.25$), suggesting poorer AS spatial accuracy in T allele carriers than non-carriers. The genotype effect on the variability of AS spatial error fell marginally short of being significant ($F[1,198] = 4.0$; $P = 0.050$; $d = 0.30$) with carriers of the risk allele having larger variability of spatial error than non-carriers. The genotype effects on the variability of AS latency ($F[1,199] = 0.01$; $P = 0.94$) and amplitude gain ($F[1,201] = 0.7$; $P = 0.39$) were not significant. There were no significant diagnosis-by-genotype interactions (all $P > 0.10$). Similar to what was seen for SNP8NRG222662, carriers of the SNP8NRG243177 risk allele generally had numerically worse AS performance (1–13%) on all variables except amplitude gain and latency variability.

## Smooth pursuit

Smooth pursuit data from four patients and two controls could not be analyzed due to poor quality. Descriptive

**Table 1** Demographic and clinical statistics by diagnosis and neuregulin-1 genotype

| Variable | Patients | | | | Controls | | | |
|---|---|---|---|---|---|---|---|---|
| | SNP8NRG222662 | | SNP8NRG243177 | | SNP8NRG222662 | | SNP8NRG243177 | |
| | G | Non-G | T | Non-T | G | Non-G | T | Non-T |
| *N* (%) | 47 (36) | 66 (64) | 64 (57) | 48 (43) | 41 (39) | 65 (61) | 57 (56) | 45 (44) |
| Male (%) | 79.5 | 67.4 | 75.0 | 70.5 | 66.7 | 61.9 | 58.3 | 70.5 |
| Mean age (SD) | 42.3 (9.7) | 40.2 (10.0) | 42.7 (9.5) | 38.8 (10.1) | 41.4 (9.5) | 40.3 (8.8) | 41.1 (8.9) | 40.3 (9.2) |
| Mean age of illness onset (SD) | 24 (6.0) | 23 (4.8) | 23 (5.8) | 22 (4.7) | | | | |
| PANSS negative symptoms (SD) | 20.2 (7.2) | 20.6 (7.4) | 19.8 (6.6) | 21.5 (8.1) | | | | |
| PANSS positive symptoms (SD) | 14.7 (5.4) | 15.1 (6.0) | 14.9 (5.3) | 15.0 (6.4) | | | | |
| PANSS general (SD) | 36.7 (9.5) | 38.8 (11.6) | 36.8 (9.6) | 39.5 (12.2) | | | | |
| PANSS total (SD) | 71.6 (18.6) | 74.5 (22.1) | 71.4 (17.8) | 76.0 (24.1) | | | | |

*PANSS* Positive and Negative Syndrome Scale

**Table 2** Descriptive statistics of antisaccade variables by diagnosis and neuregulin-1 genotype

| | Patients | | | | Controls | | | |
|---|---|---|---|---|---|---|---|---|
| | SNP8NRG222662 | | SNP8NRG243177 | | SNP8NRG222662 | | SNP8NRG243177 | |
| | G | Non-G | T | Non-T | G | Non-G | T | Non-T |
| Reflexive errors (%) | 61.1 (20.1) | 59.9 (22.9) | 61.3 (20.4) | 58.2 (23.1) | 34.1 (24.0) | 28.4 (18.2) | 33.6 (20.0) | 26.8 (19.2) |
| Amplitude gain (%) | 94.8 (30.2) | 91.6 (28.6) | 93.4 (29.2) | 91.8 (29.6) | 110.2 (27.2) | 107.1 (28.7) | 108.5 (30.4) | 109.3 (25.4) |
| Variability of amplitude gain | 49.1 (18.4) | 44.6 (19.9) | 49.7 (19.5) | 42.7 (18.3) | 48.3 (19.7) | 47.1 (18.9) | 47.0 (18.3) | 49.1 (19.5) |
| Spatial error (%) | 45.9 (12.0) | 42.1 (14.0) | 45.5 (11.8) | 41.9 (14.3) | 40.6 (16.6) | 40.3 (13.2) | 42.1 (15.6) | 39.1 (12.8) |
| Variability of spatial error | 32.1 (14.8) | 28.0 (13.4) | 31.6 (14.8) | 27.5 (13.0) | 32.2 (16.2) | 29.1 (12.1) | 32.2 (15.4) | 28.5 (11.0) |
| Latency (ms) | 339.0 (75.3) | 324.8 (78.2) | 331.9 (80.1) | 330.5 (73.7) | 296.2 (43.7) | 291.5 (41.9) | 296.2 (45.5) | 292.7 (38.9) |
| Variability of latency | 80.4 (38.4) | 70.3 (36.1) | 76.6 (40.2) | 73.3 (32.5) | 54.3 (18.6) | 56.2 (19.8) | 56.1 (20.3) | 56.4 (17.7) |

Data represent means (standard deviations) of antisaccade variables by diagnosis (patient, control) and NRG-1 genotype (SNP8NRG222662 G/non-G, SNP8NRG243177 T/non-T)

**Table 3** Descriptive statistics of smooth pursuit variables by diagnosis and neuregulin-1 genotype

| | Patients | | | | Controls | | | |
|---|---|---|---|---|---|---|---|---|
| | SNP8NRG222662 | | SNP8NRG243177 | | SNP8NRG222662 | | SNP8NRG243177 | |
| | G | Non-G | T | Non-T | G | Non-G | T | Non-T |
| Velocity gain (%) | | | | | | | | |
| 12°/s | 91.8 (10.6) | 92.9 (11.1) | 92.4 (10.5) | 92.6 (11.6) | 95.8 (8.8) | 95.1 (8.7) | 95.1 (8.7) | 95.6 (7.4) |
| 24°/s | 81.5 (6.8) | 85.6 (14.0) | 81.6 (16.9) | 87.3 (12.4) | 94.0 (13.2) | 92.8 (12.9) | 92.8 (12.9) | 92.6 (9.5) |
| 36°/s | 62.8 (21.1) | 68.9 (19.2) | 62.9 (20.7) | 71.6 (18.3) | 79.6 (17.8) | 79.3 (14.9) | 79.3 (17.8) | 79.9 (14.6) |
| Saccades (N/s) | | | | | | | | |
| 12°/s | 1.48 (0.51) | 1.56 (0.61) | 1.54 (0.55) | 1.48 (0.60) | 1.11 (0.54) | 1.20 (0.53) | 1.19 (0.59) | 1.16 (0.48) |
| 24°/s | 2.25 (0.67) | 2.34 (0.78) | 2.31 (0.66) | 2.30 (0.84) | 1.91 (0.69) | 1.84 (0.84) | 1.92 (0.75) | 1.84 (0.83) |
| 36°/s | 2.88 (0.78) | 3.01 (1.06) | 2.64 (0.87) | 2.51 (0.77) | 2.57 (0.77) | 2.60 (0.93) | 2.64 (0.87) | 2.51 (0.77) |

Data are given in means (standard deviations) for smooth pursuit variables by diagnosis (patient, control) and NRG-1 genotype (SNP8NRG222662 G/non-G, SNP8NRG243177 T/non-T)

statistics for SPEM velocity gain and saccade frequency by diagnosis and genotype are shown in Table 3. The main effects of velocity and diagnosis on SPEM velocity gain were significant and there was a significant velocity-by-diagnosis interaction (all $P < 0.001$). Velocity gain decreased with increasing target velocity, patients had lower pursuit gain than controls and the difference between patients and controls increased with increasing velocity [23]. For SPEM saccade frequency, the main effects of velocity and diagnosis were significant (both $P < 0.001$) but the velocity-by-diagnosis interaction was not significant ($P = 0.77$). The frequency of saccades increased with increasing target velocity and the patients made more saccades than controls [23].

*SNP8NRG222662*

For velocity gain, there were no significant velocity-by-genotype ($F[2,211] = 1.0$; $P = 0.35$), diagnosis-by-genotype ($F[2,211] = 0.8$; $P = 0.39$) or velocity-by-diagnosis-by-genotype ($F[2,211] = 0.9$; $P = 0.38$) interactions. At all three target velocities, the G carriers had slightly lower velocity gain (0.5–5%) than non-G carriers.

For saccade frequency, the velocity-by-genotype ($F[2,209] = 0.2$; $P = 0.77$), diagnosis-by-genotype ($F[1, 209] = 0.4$; $P = 0.54$) and velocity-by-diagnosis-by-genotype ($F[2,209] = 0.5$; $P = 0.58$) interactions were not significant. Here, the risk allele carriers had numerically fewer saccades than non-carriers at 12°/s (5%) and 36°/s (1%) but there was no difference at 24°/s.

*SNP8NRG243177*

No significant velocity-by-genotype ($F[2,206] = 2.6$; $P = 0.21$), diagnosis-by-genotype ($F[1,206] = 1.9$; $P = 0.29$) or velocity-by-diagnosis-by-genotype ($F[2,206] = 2.7$; $P = 0.13$) interactions were found for velocity gain. For all three target velocities, the risk carriers had numerically lower velocity gain than the non-carriers (0.5–7%).

For saccade frequency, there were no significant velocity-by-genotype ($F[2,203] = 0.1$; $P = 0.86$), diagnosis-by-genotype ($F[1,203] = 0.04$; $P = 0.72$) or velocity-by-diagnosis-by-genotype ($F[2,203] = 0.2$; $P = 0.80$) interactions. For all three target velocities, the carriers of the risk genotype had numerically higher saccade frequency than the non-carriers (3–5%).

## Discussion

We investigated the association between two key NRG-1 polymorphisms and performance on the AS and SPEM tasks in schizophrenia patients and healthy controls. Contrary to our hypothesis no significant genotype effects were found on any eye movement performance measures, with the exception of statistical trends for measures of AS spatial accuracy, and there were no significant diagnosis-by-genotype interactions. Patients' PANSS scores and age of illness onset were not associated with NRG-1 genotype. The study replicates previous findings of impaired AS and SPEM performance in schizophrenia patients compared to controls [62]. The subject samples were drawn from the homogenous Icelandic population [26] in which an association between NRG-1 and risk for schizophrenia has previously been demonstrated [58].

The AS and SPEM tasks are among the best validated trait markers for schizophrenia [6]. The genetic causes of AS and SPEM deficits in schizophrenia have not been fully identified but two research groups found genetic markers on chromosome 6p to be linked with impaired SPEM performance [1, 2, 39]. A study of families with schizophrenia showed linkage of a composite AS and P50 inhibitory endophenotype to a marker on chromosome 22q [42]. One study suggests that a polymorphism in the dopamine D3 receptor gene affects SPEM performance in schizophrenia patients and controls [47]. Studies of the effects of COMT val$^{158}$met polymorphism on SPEM [22, 48, 60] and AS [11, 21, 55] have not provided consistent findings. A recent study found a polymorphism in the dopamine transporter gene (DAT1) to be associated with SPEM performance, with the direction of the effect differing between healthy controls and schizophrenia patients [65]. The effects of NRG-1 genotypes on AS and SPEM have, to our knowledge, not been investigated.

We chose 2 NRG-1 SNPs; SNP8NRG222662, which is a good surrogate marker for the original core haplotype (unpublished data, deCODE Genetics) and SNP8NRG 243177 (rs6994992), which is part of the original haplotype and has been associated with inter-individual differences in a variety of measures of brain function. In a post-mortem study, the SNP8NRG243177 disease linked T allele was associated with increased expression of the NRG-1 type IV isoform in the brain of both healthy and schizophrenia subjects [35]. Hall et al. [19] found the SNP8NRG243177 T allele to be linked with decreased fronto-temporal brain activation and decreased IQ in individuals with high risk of developing schizophrenia. Furthermore, this risk allele correlated with decreased white matter density in healthy subjects [40], increased unusual thoughts in schizophrenia patients in situations of high expressed emotions [32], reduced spatial working memory [54] and higher neuroticism in healthy subjects [34] and with lowered expression of α7 nicotinic acetylcholine receptors in dorsolateral prefrontal cortex of schizophrenia patients and healthy controls [38]. The last finding is interesting in light of a recent study that found axonal expression of α7 nicotinic acetylcholine receptors on sensory neurons to be regulated by NRG-1 [20] and the α7 nicotinic acetylcholine gene is among several genes affected by a microdeletion on chromosome 15q13.3, which has recently been associated with schizophrenia [56].

The present findings do not suggest that NRG-1 is associated with neural processes critically involved in the AS and SPEM tasks. Genotypes other than NRG-1 may therefore determine AS and SPEM variance in schizophrenia and in healthy individuals. However, some small and fairly consistent differences in most AS and SPEM measures were found for both SNPs. The SNP8NRG222662 risk allele was associated with numerically worse performance on all AS measures except amplitude gain and latency variability (4–10%) and SPEM velocity gain at all three target velocities (0.5–5%). There was a trend towards G risk allele carriers having more variable spatial error than non-carriers ($P = 0.068$; $d = 0.26$). Carriers of the SNP8NRG243177 risk allele had numerically worse performance on all AS measures except amplitude gain and latency variability (1–13%) and they also had lower SPEM velocity gain (0.5–7%) and higher saccade frequency (3–5%) at all target velocities. The differences in AS spatial error ($P = 0.09$; $d = 0.25$) and spatial error variability ($P = 0.05$; $d = 0.30$) for SNP8NRG243177 fell short of being significant. AS spatial error is a measure of spatial orientation and is heavily dependent on the dorsal (magnocellular) visual stream between the visual cortex and areas of the parietal cortex [63]. Regarding the marginal *P*-values for AS spatial error, it should be mentioned that we did not correct for multiple testing. The trends for higher spatial error in risk allele carriers would not have been observed if we had applied a stringent correction for multiple testing.

The study may have lacked power to detect small genotype effects and larger subject samples might bring the differences in AS and SPEM performance to statistical significance. It is possible that the NRG-1 effects on brain function are so subtle that the eye movement measures are

not sensitive enough to detect them. Previous studies have shown significant genotype effects on brain activity measured with functional brain imaging techniques but significant effects were not observed on behavioral task performance [24, 25]. In a recent functional magnetic resonance imaging (fMRI) study of healthy subjects, COMT val$^{158}$met polymorphism was associated with frontal brain activation during the AS task but no significant COMT effects were seen on AS behavioral performance measures [11]. The small NRG-1 genotype effects on AS and SPEM performance in the present study may therefore reflect variations in brain activity, which might be detected at significant levels with functional imaging techniques such as fMRI.

The subject sample in this study was enriched for carriers of the SNP8NRG222662 risk allele. This reduces the representativeness of the sample but was necessary in order to obtain enough power for investigating the association of NRG-1 genotypes with AS and SPEM performance.

Genotypes were not associated with the patients' age of illness onset or with any PANSS symptom scores. Previous data on associations between NRG-1 and clinical measures are limited. The SNP8NRG243177 risk allele was associated with increased risk of developing psychotic symptoms in a group of young people with high genetic risk of schizophrenia [19]. A NRG-1 SNP (rs392499) was shown to be associated with positive psychotic symptoms in subjects with late onset Alzheimer's disease [15]. One study found SNP8NRG221533, which has shown strong links with the original Icelandic haplotype [57], to be associated with non-deficit schizophrenia [3]. An opposite finding was described in an Icelandic sample where the NRG-1 core haplotype was associated with deficit schizophrenia [10].

In conclusion, this first study of NRG-1 genotypes and eye movements in schizophrenia did not show significant genotype effects on AS or SPEM performance. However, risk allele carriers had numerically worse performance on most eye movement measures, especially on measures of AS spatial error. Therefore, while we can exclude a large effect, the possibility of a Type II error must be kept in mind and it remains a possibility that NRG-1 affects oculomotor endophenotypes with small effect size. Future studies of the effects of NRG-1 and other susceptibility genes for schizophrenia on eye movements should include larger but equally homogenous subject samples and should also study underlying neurophysiological measures, which may reflect gene action more directly.

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