Neuregulin 3 is associated with attention deficits in schizophrenia and bipolar disorder

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Abstract

Linkage and fine mapping studies have established that the neuregulin 3 gene (NRG3) is a susceptibility locus for schizophrenia. Association studies of this disorder have implicated NRG3 variants in both psychotic symptoms and attention performance. Psychotic symptoms and cognitive deficits are also frequent features of bipolar disorder. The aims of the present study were to extend analysis of the association between NRG3 and psychotic symptoms and attention in schizophrenia and to determine whether these associations also apply to bipolar disorder. A total of 358 patients with schizophrenia and 111 patients with bipolar disorder were included. Psychotic symptoms were evaluated using the Operational Criteria Checklist for Psychotic Illness (OPCRIT) and attention performance was assessed using the Trail Making Test (TMT). Symptoms and performance scores were then tested for association with the NRG3 variant rs6584400. A significant association was found between the number of rs6584400 minor alleles and the total OPCRIT score for psychotic symptoms in patients with schizophrenia. Moreover, in both schizophrenia and bipolar disorder patients, minor allele carriers of rs6584400 outperformed homozygous major allele carriers in the TMT. The results suggest that rs6584400 is associated with psychotic symptoms and attention performance in schizophrenia. The finding of a significant association between rs6584400 and attention performance in bipolar disorder supports the hypothesis that this NRG3 variant confers genetic susceptibility to cognitive deficits in both schizophrenia and bipolar disorder.

Received 2 November 2011; Reviewed 18 March 2012; Revised 13 April 2012; Accepted 29 May 2012; First published online 25 July 2012

Key words: Attention, bipolar disorder, cognition, neuregulin 3, psychotic symptoms, schizophrenia.

Introduction

Schizophrenia and bipolar disorder are common and debilitating disorders and each affects around 1% of the general population worldwide. Most of the variance in risk is genetic and heritabilities of ≥80% have been reported for both disorders (Cardno & Gottesman, 2000; McGuffin et al. 2003). Despite this, the identification of specific susceptibility genes has proven to be problematic. This process is particularly hampered by the phenotypic heterogeneity within each core diagnosis (Andreasen, 2000). To dissect the broad clinical phenotype into more homogeneous subphenotypes, several studies have attempted to delineate subgroups of patients according to distinct clinical symptoms, endophenotypes or statistically derived measures (Jablensky, 2006). This is exemplified by genetic studies of neuregulin 3 (NRG3), a gene that was initially reported to be associated with
the broad diagnosis of schizophrenia and was subsequently found to be associated with specific clinical symptoms and neurocognitive endophenotypes.

NRG3 is a member of the growth and differentiation factor family, which is expressed primarily in the central nervous system. Animal studies have indicated that NRG3 is critical for the development of the embryonic cerebral cortex, since it regulates cortical cell migration and patterning (Zhang et al. 1997).

Association between NRG3 and the clinical diagnosis of schizophrenia was first suggested by linkage studies. These identified a susceptibility locus for schizophrenia on chromosome 10q22-q23 in Ashkenazi Jewish (Fallin et al. 2003) and Han Chinese (Faraone et al. 2006) populations. A recent study of familial schizophrenia reported a 73.6 kb duplication in the first intron 1 of the NRG3 gene, which segregated to all affected family members (Xu et al. 2009).

Further support for the involvement of NRG3 in the pathogenesis of schizophrenia has been provided by candidate gene studies. In a Scottish sample, 10 out of 105 NRG3 single nucleotide polymorphisms (SNPs) were associated with schizophrenia; however, not one association withstood correction for multiple testing (Benzel et al. 2007) and in Han Chinese patients two out of nine NRG3 SNPs were associated with schizophrenia, but this finding still awaits replication (Wang et al. 2008).

A comprehensive fine mapping study of the 10q22-q23 region in an Ashkenazi sample revealed only associations of three out of 152 NRG3 variants and the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV; APA, 1994) diagnosis of schizophrenia not surviving correction for multiple testing (Chen et al. 2009). In the same study, applying a factor analytical approach in a family-based sample primarily revealed significant associations withstanding correction for multiple testing between a factor reflecting the extent of delusional and hallucinatory symptoms and non-coding sequence variants (rs10883866, rs10748842 and rs6584400) in intron 1 of NRG3. This finding was subsequently replicated in an independent cohort (Chen et al. 2009). These variants are located within one linkage disequilibrium (LD) block (Chen et al. 2009), rs10883866 and rs10748842 are even in allelic identity ($r^2 = 1$), next to an alternative transcription start site. This site leads to a neuronal specific NRG3 transcript, which is capable of affecting oligodendrocyte survival in vivo (Carteron et al. 2006). Two independent studies have recently confirmed the association between these NRG3 variants and both the extent of psychotic symptoms and the categorical diagnosis of schizophrenia, highlighting rs6584400 as the best supported variant (Kao et al. 2011; Morar et al. 2011). The latter replication study also reported an association between rs10748842 and rs6584400 and NRG3 expression in the human brain (Kao et al. 2011). Compared to healthy controls, schizophrenia patients displayed a pathophysiological shift in the balance of NRG3 isoforms towards more unstable NRG3 variants (Kao et al. 2011).

As cognitive impairment is a core feature in schizophrenia (Heaton et al. 2001), Morar et al. (2011) recently investigated the effect of NRG3 on cognition in patients with schizophrenia. This revealed an association between rs6584400 and rs10883866 and sustained attention, an effect that was most pronounced in patients with cognitive deficits (Morar et al. 2011). However, this association still awaits replication.

Family and twin studies have shown that relatives of index patients with bipolar disorder have an increased risk of schizophrenia and vice versa (Cardno et al. 2002; Craddock et al. 2006; Lichtenstein et al. 2009) and increasing molecular genetic evidence suggests shared susceptibility loci for schizophrenia and bipolar disorder (Purcell et al. 2009; van Snellenberg & de Candia, 2009). Further, these disorders display a remarkable similarity in their typical pattern of cognitive deficits (Schretlen et al. 2007).

Therefore, the aim of the present study was to replicate the previously reported associations of the NRG3 variant rs6584400 with the extent of psychotic symptoms and the level of attention performance in an independent cohort of schizophrenia patients. The second aim of the study was to explore if these previously reported associations in schizophrenia patients may be extended to bipolar disorder. We focused hereby on the NRG3 variant rs6584400 as this variant displayed strongest support. All replicated variants are located in one LD block. Of these, rs6584400 is the only variant for which significant association with the diagnosis of schizophrenia as well as delusional traits has been reported across studies (Chen et al. 2009; Kao et al. 2011; Morar et al. 2011).

Method

Participants

The study protocol was approved by the Ethics Committees of the Medical Faculties of the Universities of Bonn and Heidelberg. Written informed consent was obtained from all participants following a detailed explanation of the study.

We derived a total of 358 patients with schizophrenia and 111 patients with bipolar disorder, of
whom attention performance data were available from our previous genome-wide association samples (Cichon et al. 2011; Rietschel et al. 2011). All patients were recruited from consecutive hospital admissions and lifetime best estimate diagnoses were assigned according to DSM-IV criteria on the basis of multiple sources of information including structured interviews with the German version of the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID; First et al. 1998), the Operational Criteria Checklist for Psychotic Illness (OPCRIT; McGuffin et al. 1991), medical records and family history. Best estimate diagnoses were assigned by a minimum of two experienced psychiatrists or psychologists.

**OPCRIT rating**

Symptoms were coded according to the OPCRIT version 3.3.2 (McGuffin et al. 1991), a polydiagnostic 90-item checklist, which was designed for genetic research performed within the context of a collaborative study of the European Science Foundation. The checklist was completed by a trained psychologist or psychiatrist using information from the SCID-I (First et al. 1998) and clinical records. Patients were asked to recall their symptoms during illness episodes. To determine the extent of the psychotic symptoms, the sum score of the 23 binary psychotic OPCRIT items for delusions and hallucinations was calculated.

**Attention assessment**

Cognitive assessment has been performed during remission state by trained psychologists within the clinical investigations. Attention performance was assessed using the Trail Making Test (TMT; Perianez et al. 2007). This consists of two sections: (i) the TMTA, in which subjects are requested to draw lines sequentially to connect randomly distributed numbers in ascending order; (ii) the more exacting TMTB, which requires subjects to connect alternate numbers and letters. The cognitive domains that influence TMTA performance include attention, visual scanning and processing speed. These are comparable to the domains influencing the performance on the Degraded Stimulus Continuous Performance Test (CPT-DS; Nuechterlein, 1983), which was used in the study by Morar et al. (2011). The TMTB assesses cognitive flexibility and is particularly sensitive to inter-individual differences in working memory performance (Perianez et al. 2007). The TMTB:TMTA ratio score is a useful indicator of executive control function (Perianez et al. 2007). Previous reports have indicated that performance on both the TMTA ($h^2 = 0.015–0.42$; $p < 0.01$) and TMTB ($h^2 = 0.14–0.5$; Quinones et al. 2009) with the clinical diagnosis was observed in the schizophrenia sample ($p = 0.94$). A nominal association of rs6584400 with the clinical diagnosis was observed in the schizophrenia sample ($p = 0.034$) and a trend in the same direction in the bipolar disorder sample ($p = 0.104$).

### Table 1. Cognitive and demographic characteristics of schizophrenia and bipolar disorder patients

<table>
<thead>
<tr>
<th>Sample</th>
<th>Schizophrenia (N = 358)</th>
<th>Bipolar disorder (N = 111)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (yr)$^a$</td>
<td>35.78 (0.55)</td>
<td>42.30 (1.13)</td>
</tr>
<tr>
<td>Sex</td>
<td>male = 214;</td>
<td>male = 55;</td>
</tr>
<tr>
<td></td>
<td>female = 144</td>
<td>female = 56</td>
</tr>
<tr>
<td>Psychotic symptoms$^a$</td>
<td>9.29 (0.24)</td>
<td>3.41 (0.36)</td>
</tr>
<tr>
<td>TMTA (s)$^b$</td>
<td>50.00 (1.36)</td>
<td>45.81 (1.85)</td>
</tr>
<tr>
<td>TMTB (s)$^a$</td>
<td>111.69 (3.25)</td>
<td>97.27 (3.92)</td>
</tr>
<tr>
<td>TMTB/TMTA</td>
<td>2.35 (0.05)</td>
<td>2.22 (0.06)</td>
</tr>
</tbody>
</table>

TMTA, Trail Making Test A, in which subjects are requested to draw lines sequentially to connect randomly distributed numbers in ascending order; TMTB, Trail Making Test B, which requires subjects to connect alternate numbers and letters.

$^a$ Significant differences observed at $p < 0.001$.

$^b$ Significant differences observed at $p < 0.01$.

Values are mean (s.e.m.)

Lee et al. 2012; Quinones et al. 2009) and the TMTB ($h^2 = 0.14–0.5$; Quinones et al. 2009; Swan & Carmelli, 2002) is heritable. These measures are thus considered suitable phenotypes for genetic association studies. Furthermore, TMTA and TMTB scores are strong predictors of clinical outcome in patients with schizophrenia (Bowie et al. 2008). The cognitive and demographic characteristics of the present sample are presented in Table 1.

### Genotyping

Genotypic data for rs6584400 were already available, since all of the patients had participated in previous genome-wide association studies of schizophrenia and bipolar disorder (Cichon et al. 2011; Rietschel et al. 2011). Genome-wide genotyping had been performed on HumanHap550v3 BeadArrays using the Infinium II assay (Illumina, USA). The allele frequency of rs6584400 in the total sample was in the Hardy–Weinberg equilibrium ($\chi^2 = 0.006$; degrees of freedom = 1; $p = 0.94$). A nominal association of rs6584400 with the clinical diagnosis was observed in the schizophrenia sample ($p = 0.034$) and a trend in the same direction in the bipolar disorder sample ($p = 0.104$).

### Data analysis

The SPSS software (version 18.0, SPSS Inc., 2007) was used for quantitative analyses. Spearman correlations
were computed to assess the association between the rs6584400 genotype and the total OPCRIT score for psychotic symptoms. Since the previously reported association between NRG3 and attention was driven primarily by patients with cognitive deficits, analyses of variance were performed to compare TMT scores across the following samples: (i) all patients with schizophrenia or bipolar disorder, with the exception of those with good performance, as defined by TMT scores not lower than 1 S.D. below the mean for the general population (Tombaugh, 2004); (ii) the total schizophrenia sample or the total bipolar disorder sample; (iii) a pooled sample including all patients. Subsample (i) is subsequently referred to as the cognitive (−) sample. Adjustment was made for age, which had a substantial influence on TMT performance and which differed significantly between the schizophrenia and bipolar disorder samples (Table 1), and p values were corrected for multiple comparisons (Bonferroni’s method). To confirm the comparability of the TMT and CPT, we assessed the correlation of the performances on these tests in a subsample of 20 schizophrenia patients who completed both tasks. Further, we explored differences of probable confounding variables between NRG3 genotypes such as medication (antipsychotics, antidepressants and tranquilizers) and response to medication according to the OPCRIT criteria as well as education and severe cognitive impairment. Education was defined as years of school and professional education. To evaluate cognitive abilities, we employed the mini-mental state examination. Although this determines the presence of severe cognitive impairment, it does not reveal low-grade cognitive deficits (Folstein & McHugh, 1975).

## Results

### Association analysis of diagnosis clinical features

The total OPCRIT score for psychotic symptoms was significantly correlated with the number of minor alleles of rs6584400 in the schizophrenia sample ($r = 0.110; p = 0.037$). No such correlation was observed in the bipolar disorder sample ($r = 0.014; p = 0.885$). The association between rs6584400 and the extent of psychotic symptoms was in the same direction as that reported by Morar et al. (2011). The patients were therefore subdivided into minor allele carriers (GA + AA) and homozygous major allele carriers (GG) of rs6584400 for the subsequent analysis of association between rs6584400 and attention.

### Association analysis of the TMT

As reported previously (Schretlen et al. 2007), patients with bipolar disorder completed the TMTA ($F = 11.3; p = 0.001$) and the TMTB ($F = 16.7; p < 0.001$) significantly faster than patients with schizophrenia (Table 1). In the schizophrenia cognitive (−) sample, rs6584400 minor allele carriers (GA + AA) completed both the TMTA ($F = 3.9; p = 0.025$, corrected $p < 0.05$) and the TMTB ($F = 4.3; p = 0.020$, corrected $p < 0.05$) significantly faster than homozygous major allele carriers (GG; Table 2). Similarly, minor allele carriers in the bipolar disorder cognitive (−) sample, performed

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**Table 2. Association between rs6584400 and Trail Making Test A (TMTA) and B (TMTB) scores in patients with schizophrenia and bipolar disorder**

<table>
<thead>
<tr>
<th>Samples</th>
<th>Number of patients</th>
<th>Genotypes</th>
<th>TMTA</th>
<th>TMTB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Mean ± S.D.</td>
<td>p</td>
</tr>
<tr>
<td>Total schizophrenia sample</td>
<td>358</td>
<td>GA + AA 81</td>
<td>102.5 ± 50.5</td>
<td>0.023*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GG 277</td>
<td>114.4 ± 64.2</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia cognitive(−) sample</td>
<td>303</td>
<td>GA + AA 68</td>
<td>109.5 ± 51.3</td>
<td>0.025*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GG 235</td>
<td>124.4 ± 63.9</td>
<td></td>
</tr>
<tr>
<td>Total bipolar disorder sample</td>
<td>111</td>
<td>GA + AA 35</td>
<td>84.3 ± 36.9</td>
<td>0.007*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GG 76</td>
<td>103.2 ± 42.1</td>
<td></td>
</tr>
<tr>
<td>Bipolar disorder cognitive(−) sample</td>
<td>93</td>
<td>GA + AA 28</td>
<td>87.3 ± 39.2</td>
<td>0.009*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GG 65</td>
<td>109.5 ± 41.1</td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>469</td>
<td>GA + AA 116</td>
<td>87.3 ± 39.2</td>
<td>0.001*</td>
</tr>
<tr>
<td></td>
<td></td>
<td>GG 353</td>
<td>109.5 ± 41.1</td>
<td></td>
</tr>
</tbody>
</table>

N: Number of patients, TMTA, Trail Making Test A, in which subjects are requested to draw lines sequentially to connect randomly distributed numbers in ascending order; TMTB, Trail Making Test B, which requires subjects to connect alternate numbers and letters.

* Significance observed at corrected $p < 0.05$. 

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both the TMTA (F = 5.8; p = 0.009, corrected p < 0.05) and the TMTB (F = 4.9; p = 0.015, corrected p < 0.05) significantly faster than homozygous major allele carriers. The differences in TMTA performance remained significant in both total samples (schizophrenia: F = 4.0; p = 0.023, corrected p < 0.05; bipolar disorder: F = 6.3; p = 0.007, corrected p < 0.05). In the pooled sample, differences in TMTA (F = 9.2; p = 0.001 corrected p < 0.01) and TMTB performance (F = 7.3; p = 0.004, corrected p < 0.01; Table 2) reached significance. However, the differences in TMTB performance only achieved significance in the total bipolar disorder sample (F = 4.7; p = 0.016, corrected p < 0.05). In the total schizophrenia sample, the association with TMTB did not withstand correction for multiple testing (F = 3.4, p = 0.034, corrected p > 0.05). We hypothesized that this may be attributable to the task-switching component of the TMTB measuring executive control (Perianez et al. 2007). In contrast to fundamental attention abilities, executive control may not be associated with the NRG3 variant rs6584400. To test this hypothesis, we investigated the association between rs6584400 and the TMTB:TMTA ratio, which has been described as one of the best indicators of executive control function (Perianez et al. 2007). No significant association with the TMTB:TMTA ratio score was found in any of the five samples (all p > 0.3). Inclusion of the total OPCRIT score for psychotic symptoms as a covariate did not substantially alter the association findings for NRG3 and TMT performance. In a subsample of 20 schizophrenia patients, performances on the TMT correlated significantly with the performance on the CPT (TMTA: r = 0.430; p = 0.029; TMTB: r = 0.481; p = 0.016). In the total sample we observed no differences between rs6584400 minor allele carriers (GA + AA) and homozygous major allele carriers (GG) in medication (antipsychotics; χ² = 0.6, p = 0.70, antidepressants: χ² = 1.8, p = 0.24, tranquilizers: χ² = 0.6, p = 0.45) or response to medication (χ² = 0.04, p = 1.0), education (F = 6.7; p = 0.09) and current mini–mental state scoring (F = 0.4; p = 0.25).

Discussion

The aim of the present study was to investigate the association of the NRG3 variant rs6584400 with attention performance and psychotic symptoms in schizophrenia and bipolar disorder. In the German sample, a significant association was observed between rs6584400 and the total OPCRIT score for psychotic symptoms in schizophrenia patients and this represents an independent replication of the findings of previous studies (Chen et al. 2009; Morar et al. 2011). No such association was observed in the bipolar disorder sample. As expected, bipolar disorder patients displayed fewer psychotic symptoms than schizophrenia patients and thus an association between the number of minor alleles of rs6584400 and the total OPCRIT score for psychotic symptoms may have been overlooked.

The major finding of the present study was the robust association between rs6584400 and attention. The direction of this association was the same in patients with schizophrenia and bipolar disorder. Minor allele carriers of rs6584400 completed the TMTA and TMTB faster than homozygous major allele carriers. The most significant association finding was observed in the pooled sample, which included all patients. The results indicate that the association between NRG3 and attention is not specific to schizophrenia and can be extended to bipolar disorder. Associations were more consistent for the TMTA than for the TMTB. This may be attributable to differences in the complexity of the tasks involved in the TMTB and the TMTA. As an indicator of cognitive flexibility, the TMTB involves task switching, which reflects executive control (Perianez et al. 2007). The fact that no significant association was observed between rs6584400 and the TMTB:TMTA ratio measuring executive function supports our hypothesis. This suggests that, in the present study, NRG3 was predominantly associated with basic attentional processes. This is consistent with the finding of a previous study (Morar et al. 2011). The inclusion of psychotic symptoms as a covariate did not alter these results, indicating that the putative effect of rs6584400 on cognitive function is independent of psychotic symptoms.

In the subsequent association analysis, patients without cognitive deficits were excluded. For the bipolar disorder patients, this second analysis yielded almost identical results. In the schizophrenia patients with cognitive deficits, the association of rs6584400 was significant for both TMTA and TMTB. In the total schizophrenia sample, only the association with TMTA was statistically significant. This is consistent with the finding of Morar et al. (2011), who also reported a more pronounced association between schizophrenia and sustained attention in subjects with cognitive deficits.

In their study Morar et al. (2011) employed the CPT-DS to measure attention. This test can be considered comparable to the TMT as in our study performance of CPT correlated significantly with performances on the TMTA and TMTB. The TMT and CPT are described as the most sensitive instruments to measure attention deficits in psychiatric disorders (Fröstl, 2005). Both
tests have been reported to assess even subtle differences (Asarnow et al. 2002). TMT and CPT-DS are considered ‘frontal’ tests as performance on these tests majorly depends on frontal cortex functioning (Fallgatter & Strik, 2000; Nakamura et al. 2008). Furthermore, the metabolism of the neurotransmitter dopamine, which is centrally involved in attention regulation, has been described to correlate with scores of TMT and CPT-DS (Vernaleken et al. 2007).

Interestingly, although minor allele carriers in the schizophrenia sample displayed more psychotic symptoms, they performed faster on TMT sections A and B and this was particularly pronounced in patients with a relatively poor cognitive performance. This may indicate that rs6584400 is a protective factor in individuals with clinical deficiency by boosting cognitive performance, as suggested previously (Morar et al. 2011). These results are also consistent with studies reporting higher cognitive functioning in schizophrenia patients who have more pronounced psychotic symptoms (Hallmayer et al. 2005; Jablensky, 2006).

The direction of the association between the minor allele of the NRG3 variant rs6584400 and the extent of psychotic symptoms varies across studies (Chen et al. 2009; Kao et al. 2011; Morar et al. 2011). Possible explanations for this include differences in the clinical and neurocognitive characteristics of the samples investigated, as well as differences in environmental and genetic background. In the present sample, the association with the extent of psychotic symptoms was in the same direction as that reported by Chen et al. (2009) and Morar et al. (2011), thus providing independent evidence for these previous findings.

Another member of the NRG family is NRG1. This is a paralogue of NRG3 and has been reported to be associated with schizophrenia by several groups (Munafò et al. 2006). NRG1 has also been proposed as a susceptibility gene for bipolar disorder (Georgieva et al. 2008) and NRG1 variants have been reported to be associated with attention performance (Stefanis et al. 2007). These findings provide support for the hypothesis that the NRG pathway is involved in the development of psychiatric disorders.

Although further studies are necessary to elucidate the role of NRG3 in attention and clinical features within the context of psychiatric disorders, the present results provide independent support for the previously reported association between NRG3 and the extent of psychotic symptoms and attention performance in schizophrenia. The present study has also demonstrated that this effect is not disease-specific, since a similar association was observed in patients with bipolar disorder. Although patients with bipolar disorder and schizophrenia differ in terms of the level of neuropsychological deficits (Schretlen et al. 2007), as observed in the present study, some of the underlying biological pathways may be common to both disorders. The present results suggest that NRG3 is implicated in the pathogenesis of schizophrenia and bipolar disorder via cognitive impairment. Given that cognitive measures predict clinical outcome (Bowie et al. 2008), this phenotype may have implications for future research into novel treatment strategies. Future studies should also explore whether the NRG3 association with attention extends to other psychiatric disorders.

Acknowledgements

We are grateful to all of the patients who contributed to this study. We also thank the probands from the community-based cohorts of PopGen, KORA and the Heinz Nixdorf Recall (HNR) study. This study was supported by the German Federal Ministry of Education and Research (BMBF) within the context of the National Genome Research Network plus (NGFNplus) and the MooDS-Net (grant 01GS08144 to S.C. and M.M.N.; grant 01GS08147 to M.R.). M.R. was also supported by the 7th framework programme of the European Union (ADAMS project, HEALTH-F4-2009-242257). M.M.N. also received support from the Alfried Krupp von Bohlen und Halbach-Stiftung. J.S. was supported by the German Research Foundation (GRK 793).

Statement of Interest

None.

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Neuregulin 3 affects attention performance


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