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# *BDNF* and *NRG1* polymorphisms and temperament in selective serotonin reuptake inhibitor-treated patients with major depression

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**ABSTRACT**

**Objective:** We investigated the separate effects of and possible interactions between the functional polymorphisms of brain-derived neurotrophic factor (*BDNF)* rs11030101, *BDNF* rs61888800, and neuregulin-1 (*NRG1)* rs3924999 and *NRG1* rs6994992 on change of temperament scores in a clinical sample of subjects with major depression (MDD), who received selective serotonin reuptake inhibitor (SSRI) treatment for a period of six weeks.

**Methods:** The study population consisted of 98 Finnish individuals with MDD. They were assessed by the 107-item Temperament and Character Inventory (TCI) temperament questionnaire (version IX) and the Montgomery-Åsberg Depression Rating Scale (MADRS). In general linear univariate models (GLM) for Novelty Seeking (NS) or Reward Dependence (RD) change age, gender, MADRS score change and *BDNF* and *NRG1* genotypes were used as explaining explanatory variables.

**Results:** Mean comparisons between corresponding temperament dimensions and genotypes showed significant differences between NS change and *BDNF* rs61888800 T-carrying status (mean difference: GG 0.30, GT/TT 2.47, p=0.022, T-test) and between RD change and *NRG1* rs3924999 A-carrying status (mean difference: GG 1.21, GA/AA -0.33, p=0.003). In GLM models for NS change the significant predictors comprised *BDNF* rs61888800 T-carrying status, age and MADRS score change (model 1), and additionally *NRG1* rs6994992 T-carrying status (model 2). For RD change the predictors included *NRG1* rs3924999 A-carrying status, age and MADRS score change (model 1) and additionally gender (model 2).

**Conclusion:** According to the current results both *BDNF* and *NRG1* are associated with temperament traits during depression. These results warrant further studies regarding the impact of this association on depression recovery.

KEYWORDS: Brain-Derived Neurotrophic Factor, Neuregulin-1, Depression, Temperament

SIGNIFICANT OUTCOMES

The T-carriers of *BDNF* rs61888800 had a more favourable temperament change on the NS dimension towards recovery than did the GG-carriers. For *NRG1* rs3924999, the GG genotype showed a more favourable change in RD than the A-carriers.

LIMITATIONS

Small study sample, lack of replication sample, relatively short follow-up time and single-nucleotide polymorphism (SNP) analyses are the limitations of the present study.

**INTRODUCTION**

The diagnosis of major depression (MDD) has been defined as a cluster of specific symptoms, including among others depressed mood, anhedonia and lack of energy, but the clinical features of an individual patient are heterogeneous and therefore prediction of treatment response is challenging. There is a need for biological markers as outcome measures, because currently used depression measures are based on reporting of clinical symptoms, while each measure has its limitations and therefore measuring outcome lacks accuracy.

Temperament patterns can be observed since early infancy and have been associated with thickness of cortex in infants (1). Brain-derived neurotrophic factor (BDNF) is a protein involved in the proliferation, differentiation and survival of neuronal cells and in the regulation of synaptic plasticity and connectivity in the adult brain, and BDNF has been associated with personality traits, temperament and depression (2, 3). BDNF also has a possible role in regulating interactions between neurons and microglia (4). Neuregulin-1 (NRG1) is a neurotrophic factor that has been associated with treatment response to serotonin selective antidepressive agents in MDD and with the risk of major depression (5, 6). NRG1 has been found to induce activation in tropomyosin-related kinase B (TrkB), which is a receptor of BDNF, and the receptor has been found to mediate neural plasticity and is also reportedly involved in the mechanisms of action of antidepressive drugs (7). Both NRG1 and BDNF induce myelination in the central nervous system by oligodendrocytes through increasing N-methyl-D-aspartate (NMDA) receptor currents (8). We wanted to investigate the association between both neurotrophic factors BDNF and NRG1 and temperament in presence of major depressive disorder.

Temperament has in general been defined as the innate part of the human personality as opposed to learned features (9). Cloninger developed a psychobiological personality model describing four dimensions of temperament, namely Harm Avoidance (HA), Novelty Seeking (NS), Reward Dependence (RD) and Persistence (P). The temperament dimensions in Cloninger's model are suggested to present different dimensions of automatic neural responses possibly associated with specific monoaminergic activity (10).

According to a meta-analysis patients with major depressive disorder have been shown to have higher score in Harm Avoidance and lower scorers in the other three temperament dimensions (11). More specifically, the Harm Avoidance score level has showed to be inversely associated with euthymia in depressive disorder (11). The relationship between temperament and depression has been supported in a number of studies as an association with the risk of depression, risk of recurrence and impact on treatment response (11-20). According to many studies the temperamental changes during recovery from depression include a marked decrease in HA and to some extent an increase in RD (21).

Since the temperamental traits during depressive state can be regarded as a result of abnormal neuronal processing, this abnormality could be a consequence of a genetic vulnerability in the genes involved in neural regeneration mechanisms. Several single-nucleotide polymorphisms (SNPs) in *BDNF* gene have been associated with antidepressant response (22). The *BDNF* gene has been suggested to have an important role in the pathogenesis of depression, and moreover in neurogenesis and synaptogenesis during antidepressant drug treatment (7,23). The rs11030103 has been associated with major depression (22), but in other studies no association was found (24,25). In another study rs11030103 of *BDNF*, but not rs61888800, was found to be associated with a change in MADRS score among patients receiving electroconvulsive therapy (ECT) (26). The rs11030101 of *BDNF* has been reported to be associated with depression and the rs61888800 of *BDNF* with better response to antidepressant treatment (22), although other studies did not support this finding (24, 27). *NRG1* has been found to have an important function in neurodevelopment, neurotransmission and synaptic plasticity (28). In a large case-control study, rs 3924999 and several other *NRG1* SNPs and haplotypes have been associated with the risk of major depression, bipolar disorder and schizophrenia (6). The rs6994992 of NRG1 has been associated to depression symptom severity, psychotic symptom patterns and alcohol use disorders (29,30).

Studies exploring associations between temperament and genetic variations in *BDNF* or *NRG1* in major depression are so far rare. Mandelli *et al.* in a sample of 86 bipolar spectrum depressed patients reported both *BDNF* haplotype of SNPS rs6265 and rs11030104 (A-C) and higher HA score to be associated with

poorer six-month treatment response, but HA scores were not associated with these *BDNF* genotypes (31). In a meta-analysis *NRG1* was found to potentially affect selective serotonin reuptake inhibitor (SSRI) treatment and NRG1 has been suggested to be a biomarker for depression (5).

We investigated the separate effects of and possible interactions between functional polymorphisms *BDNF* rs11030101, *BDNF* rs61888800, *NRG1* rs3924999 and *NRG1* rs6994992 polymorphisms on changes in temperament dimension scores (HA, NS, RD, P) assessed by the Temperament and Character Inventory (TCI) in a clinical sample of subjects with major depression, who received SSRI-treatment for a period of six weeks.

## METHODS

### Study subjects and clinical intervention

The study population consisted of 98 Finnish individuals 19-72 years of age (41 males and 57 females, mean age [SD] 40.5 [14.1] years). All subjects were patients in secondary outpatient services in Pirkanmaa Hospital District, Finland (total catchment population approximately 300,000). The inclusion criteria were: 1) current episode of major depressive disorder according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) criteria and 2) a Montgomery-Åsberg Depression Rating Scale (MADRS) (32) score of at least 20. The doses of the study medication were adjusted according to the clinical response, which was checked during a visit after three weeks of treatment. Medication adherence was self-monitored by keeping a paper-and-pencil medication diary. We considered an adherence rate of at least 80 % as adequate treatment. Each patient was interviewed by clinical researchers, who were all experienced psychiatrists before the initial assessment for the study. In the initial assessment the DSM checklist for the MDD was fulfilled for each patient. Major somatic diseases, with medications potentially causing depression, bipolar disorder, schizophrenia, severe personality disorders or disorders related to substance abuse were considered as exclusion criterion. Patients treated for previous depressive episodes had to be free from antidepressants for the past three months, and mood stabilizing or antipsychotic medications were not allowed. Anxiolytics and hypnotics in minor doses were permitted at the early stage of the study.

Most of the patients (n=80, 81%) had no history of previous depressive episodes *vs* patients with previous depressive episodes (n=18, 18.4%).

The Temperament and Character Inventory (TCI) is a questionnaire developed to distinguish the four dimensions (9). For assessment of temperament dimensions all study subjects completed the 107-item TCI temperament questionnaire (version IX) in the presence of clinical researcher and MADRS interview was performed at the initial assessment of the study and after six weeks of follow-up. For six weeks the patients received SSRI medication, citalopram, fluoxetine or paroxetine (the three most frequently prescribed SSRIs in Finland at the time the study). Citalopram was used by 51 patients (52.0%), fluoxetine was by 35 patients (35.7%), and paroxetine by 12 patients (12.2%). Out of 57 females 26 (45.6%) were using citalopram, 22 (38.6%) fluoxetine and 9 paroxetine (15.8%). Out of all males 25 (61%) were using citalopram, 13 (31.7%) fluoxetine and 3 (7.3%) paroxetine. The treatment response was determined as at least 50% MADRS score reduction. All subjects gave written informed consent and the local ethics committee approved the study protocol.

DNA extraction and *BDNF* rs11030101, *BDNF* rs61888800, *NRG1* rs3924999 and *NRG1* rs6994992 genotyping

Genomic DNA was extracted from peripheral blood leucocytes using the QIAamp DNA Blood Minikit and automated biorobot M48 extraction (Qiagen, Hilden, Germany). *BDNF* gene alterations rs11030101 and rs61888800 were genotyped using Taqman SNP Genotyping Assays C___1751785_10 and C__89097203_10 respectively and the ABI Prism 7900HT Sequence Detection System (Applied Biosystems, Foster City, California, USA). Ten random samples were run as duplicates. No discrepancies were found.

Statistical methods

MADRS baseline and endpoint scores were compared between the studied genotypes by using ANOVA. For exploratory analysis, Pearson's correlations between *BDNF* and *NRG1* genotypes and scores for changes in temperament dimensions from baseline to six weeks were calculated to select the temperament dimensions for the general linear univariate model (GLM). T-test was used in the calculation of mean

differences between temperament score changes between the *BDNF* and *NRG1* genotype groups. GLM models were used to predict NS and RD change. These models were adjusted for age, gender and MADRS score change, and *BDNF* and *NRG1* genotypes were used as explanatory variables.

**RESULTS**

The genotype distributions of both *BDNF* and *NRG1* SNPs according to temperament dimensions and MADRS scores at baseline and endpoint are presented in Table 1. At six weeks 88 patients completed the TCI questionnaire and 87 the MADRS interview. *BDNF* rs11030101 genotyping failed in one patient. There were no significant differences in MADRS baseline or endpoint scores between any of the study genotypes (ANOVA). MADRS baseline or endpoint scores did not show significant correlations with temperament change scores, except for ΔHA (r=0.36, p=0.001) at endpoint.

The correlation between *BDNF* rs61888800 T-carrying status and change in NS scores from baseline to six weeks was significant (r=0.23, p=0.034). A negative significant correlation was found between *NRG1* rs3924999 A-carrier status and RD change (r=-0.29, p=0.005).

Mean comparisons between corresponding temperament dimensions and genotypes revealed significant differences between NS change and *BDNF* rs61888800 T-carrying status (mean difference: GG 0.30, GT/TT 2.47, p=0.022, T-test) and between RD change and *NRG1* rs3924999 A-carrying status (mean difference: GG 1.21, GA/AA -0.33, p=0.003), but not between baseline or six-week NS score and *BDNF* genotype, or RD baseline or six-week score and *NRG1* genotype.

In GLM for NS and RD change age, gender, MADRS score change and *BDNF* or *NRG1* genotypes were used as explanatory variables. The best fitting models for NS change comprised *BDNF* rs61888800 T-carrying status, age and MADRS score change (model 1). This model explained 11.8% of the variance of the NS-change ($\eta p^2 = 0.118$) and when NRG1 T-carrying status was added to the model (model 2), it explained 15.1% of NS change ($\eta p^2 = 0.151$). For RD change the best fitting models included *NRG1* rs3924999 A-

carrying status, age and MADRS score change (model 1). This model explained 14.9% of the variance of RD-change ($\eta p^2$ =0.149) and when gender was added to the model (model 2), it explained 16.9% ($\eta p^2$=0.169) of the RD change. The results of the GLM models are presented in Table 2.

**DISCUSSION**

In this study we explored changes in temperament dimension scores at the acute stage of depression during six-week treatment with SSRI. We also analysed the levels of depressive symptoms before and after acute phase treatment between the BDNF and NRG1 genotypes. We found the T-carriers of *BDNF* rs61888800 to show an increase in NS score. The outcome measured with MADRS score change also had an effect on this difference in the multivariate analysis. Additionally, patients with GG-genotype in *NRG1* rs3924999 showed an increase in RD score during treatment, but the A-carriers did not show a similar change. For this difference the outcome did not have any effect in the multivariate analysis. We neither found any genotype effects in baseline or endpoint depression severity.

There are so far no studies on the relationship between NS change and *BDNF* genotypes. HA levels were not associated with the present *BDNF* or *NRG1* genotypes. Earlier studies have reported somewhat contradictory results on the relationship between HA, *BDNF* genotypes or serum concentrates. Kim *et al.* found *BDNF* Val/Val genotype of Val66Met polymorphism to be associated with higher HA after negative life stressors in a community sample (33), whereas Minelli *et al.* found Met-carriers of *BDNF* Val66Met genotype to have higher BDNF serum levels (34). In a study on healthy Caucasian subjects the Met/Met genotype of *BDNF* Val66Met polymorphism was associated with higher scores on Harm Avoidance subscales HA1 (anticipatory worry) and HA2 (uncertainty) (35), and in another study on healthy subjects the same genotype was associated with low HA total scores (36). A meta-analysis including 607 patients showed no association between *BDNF* Val66Met and HA (37).

For the RD it is noteworthy that the changes in RD during recovery from depression have been found to be small in magnitude. During major depression increase in RD scores has been reported (21), and in general

sample studies there are findings of low RD being associated with risk of depression (10,38), and also with risk of suicide attempts (18). It is possible that the negative findings related to depression state-dependency of RD are associated with 1) the small magnitude of the change and 2) different onset time of change in different patients. According to the present finding the patients with *NRG1* rs3924999 GG-genotype could represent a subpopulation with a relatively rapid recovery from the depressive state dependent changes in RD and the A-allele carriers may refer to prolonged trait-related changes. Verifying this hypothesis requires replication of the analysis in a larger sample and with a longer follow-up. The subscales RD2-RD4 are all related to social sensitivity, and the low RD score in depression could reflect the anhedonic state and result in impaired ability in social functioning. In animal models NRG1 has been reported to be associated with amygdala activation (39).

*BDNF* and *NRG1* genotypes may be associated with alterations in the brain neurotransmission system during recovery from depression. The increase in NS scores among the T-carriers of *BDNF* rs61888800 during the six weeks of treatment with SSRIs can be viewed as an expected change, because NS scores usually decrease during depressive state. Among GG genotype of *BDNF* rs61888800 there seems to be a delay in recovery from depressive trait as measured by NS. However, over six weeks there were no differences in absolute response between these genotypes.

There is evidence from earlier research of lower NS and RD scores during depressive state (11) and of an increase of NS scores during recovery (40). According to the present results we could assume that the T-carriers of *BDNF* rs61888800 undergo a more favourable temperament change towards recovery when compared to GG-carriers, who showed no change in NS scores. For *NRG1* rs3924999, GG genotype had a more favourable change to RD than the A-carriers. The same result was obtained for both *BDNF* and *NRG1* genotypes using multivariate analysis considering confounding factors age and gender and treatment response in the model. Age and gender did not have any effect on the results of the multivariate analysis. According to Cloninger, temperament dimensions tend to be relatively stable throughout the life span, although some studies, e.g. Brändström *et al.,* have found associations between age, gender, NS scores as well as RD scores in general population (41).

The possible functional mechanism underlying the results may be differences in expression in brain of the genes studied. T-carriers of BDNF rs6188880 have been found to have lower expression of BDNF in frontal cortex and higher expression in cerebellum, and there is an increasing trend for the T-allele expression in putamen. No difference has been found in the expression of *NRG1* rs3924999 between different brain regions (42). The interplay between 5-HTTLPR and BDNF has been found to contribute for the risk of major depressive disorder especially in presence of stressful life events (43). We have earlier showed the SERT ss-allele to associate with higher Persistence (P) scores in depression (44). However, in the present study our primary aim was to explore the possible interactions between BDNF and NRG1.

All patients included had an MDD episode of at least moderate severity. The dosage and adherence to antidepressant medication were monitored during the follow-up period. The ethnic background of the sample was homogenous. We chose the observation period of six weeks in order to better detect a possible change in temperament profile as in general acute phase SSRI medication trials should last at least four to six weeks (45). Due to the small sample size there is a risk of both type 1 and type 2 errors. The current results should be considered as preliminary, and need to be replicated in other samples.

According to the present results, both *BDNF* and *NRG1* are associated with temperament traits during depression and may influence recovery from clinical depression.

**AUTHORS' CONTRIBUTIONS**

Drs. Kampman, Illi and Leinonen were responsible for the study design planning. Drs. Setälä-Soikkeli, Viikki, Kampman, Illi and Leinonen participated in patient recruitment. Drs. Mononen and Lehtimäki planned and performed the genotyping. Drs. Andre and Kampman performed the statistical analyses and prepared the first draft of the manuscript. All authors commented and accepted the final manuscript.

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**STATEMENT OF INTEREST**

None.

**ETHICAL STANDARDS**

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

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Table 1. The genotype distributions of both BDNF and NRG1 SNPs according to temperament dimensions and MADRS scores at baseline and endpoint.

| | **All patients (n=98 baseline, n=88 endpoint)** | **BDNF rs11030101 (n=97 baseline, n=87 endpoint)** | | | **BDNF rs61888800 (n=98 baseline, n=88 endpoint)** | | | **NRG1 rs3924999 (n=98 baseline, n=88 endpoint)** | | | **NRG1 rs6994992 (n=98 baseline, n=88 endpoint)** | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Temperament dimension (mean + SD) | | TT (n=23) | TA (n=46) | AA (n=57) | GG (n=3) | GT (n=23) | TT (n=7) | GG (n=40) | GA (n=47) | AA (n=11) | CC (n=32) | CT (n=53) | TT (n=13) |
| Novelty seeking baseline | 19.6 ±7.5 | 19.5 ±6.9 | 20.8 ±7.6 | 17.4 ±7.7 | 19.9 ±7.1 | 19.7 ±7.4 | 16.0 ±10.6 | 18.3 ±7.4 | 19.4 ±6.7 | 25.0 ±9.2 | 20.2 ±6.7 | 18.8 ±7.5 | 21.4 ±9.4 |
| Novelty seeking endpoint | 20.9 ±7.4 | 20.9 ±6.8 | 21.5 ±7.7 | 20.0 ±7.7 | 20.4 ±6.9 | 21.9 ±7.6 | 19.2 ±10.7 | 20.0 ±7.0 | 20.6 ±7.2 | 25.2 ±8.8 | 20.5 ±6.9 | 20.4 ±7.3 | 23.4 ±8.8 |
| Harm avoidance baseline | 23.6 ±7.0 | 23.1 ±6.8 | 23.8 ±7.9 | 24.0 ±5.5 | 24.1 ±6.4 | 22.5 ±7.6 | 25.7 ±8.3 | 25.6 ±6.3 | 22.1 ±7.2 | 23.2 ±6.6 | 24.2 ±6.8 | 24.1 ±6.9 | 20.3 ±6.9 |
| Harm avoidance endpoint | 21.8 ±8.0 | 21.6 ±7.2 | 22.7 ±8.9 | 20.6 ±7.0 | 23.1 ±6.6 | 20.0 ±9.8 | 21.3 ±7.4 | 22,6 ±8,3 | 20.7 ±7.9 | 23.2 ±6.4 | 22.4 ±8.4 | 22.5 ±7.9 | 17.8 ±6.2 |
| Reward dependency baseline | 15.5 ±4.0 | 15.6 ±4.6 | 15.6 ±3.8 | 15.4 ±3.7 | 15.8 ±3.9 | 15.4 ±4.1 | 14.1 ±3.1 | 14,7 ±4,1 | 15.9 ±3.8 | 17.2 ±3.0 | 16.0 ±3.8 | 15.5 ±4.2 | 14.8 ±3.2 |
| Reward dependency endpoint | 16.0 ±3.7 | 15.6 ±4.0 | 16.1 ±3.9 | 15.9 ±3.3 | 16.1 ±3.8 | 15.7 ±3.8 | 16.2 ±3.3 | 15,8 ±3,3 | 15.7 ±4.0 | 17.4 ±4.3 | 16.0 ±3.7 | 16.3 ±3.9 | 14.5 ±2.6 |
| Persistence baseline | 4.4 ±2.1 | 3.6 ±1.7 | 4.4 ±2.1 | 5.0 ±2.1 | 4.3 ±2.2 | 4.4 ±1.9 | 5.4 ±1.4 | 4,2 ±2,1 | 4.6 ±2.0 | 4.3 ±2.1 | 4.6 ±1.9 | 4.2 ±2.2 | 4.9 ±1.8 |
| Persistence endpoint | 4.4 ±2.1 | 4.2 ±1.8 | 4.0 ±2.2 | 5.0 ±2.0 | 4.3 ±2.0 | 4.2 ±2.1 | 6.0 ±1.4 | 4,1 ±2,2 | 4.6 ±2.0 | 4.3 ±1.9 | 4.8 ±2.1 | 4.1 ±2.0 | 4.7 ±2.1 |
| MADRS baseline score (mean + SD) | 27.0 ±5.6 | 28.4 ±5.2 | 26.0 ±5.7 | 28.0 ±6.0 | 26.7 ±5.3 | 27.8 ±5.7 | 27.9 ±9.0 | 28,6 ±5,4 | 26.1 ±5.9 | 26.6 ±5.6 | 27.3 ±6.4 | 26.9 ±5.7 | 27.9 ±4.3 |
| MADRS endpoint score (mean + SD) | 12.2 ±8.2 | 12.4 ±8.2 | 12.6 ±8.4 | 11.3 ±8.3 | 12.3 ±7.9 | 11.9 ±8.5 | 12.3 ±10.3 | 12,1 ±8,5 | 12.4 ±8.7 | 11.3 ±5.0 | 11.7 ±8.8 | 12.1 ±7.8 | 13.1 ±8.7 |

Table 2. Results of the two ANCOVA models, in which temperament dimension changes (endpoint-baseline) of NS and RD were used as target variables and BDNFrs61888800 and NRG1rs6994992 or NRG rs3924999 genotypes as factors and MADRS score change and age as covariates.

| | Novelty seeking change | | | Reward dependency change | | |
|---|---|---|---|---|---|---|
| | $\eta p^2$ | p | power | $\eta p^2$ | p | power |
| Complete model | 0.151* | 0.019 | 0.82 | 0.169 | 0.009 | 0.876 |
| Explaining variable | | | | | | |
| BDNF rs61888800 GG/T-carriers | 0.057 | 0.029 | | | | |
| NRG1 rs6994992 CC/T-carriers | 0.036 | 0.088 | | | | |
| NRG1 rs3924999 GG/A-carriers | | | | 0.076 | 0.012 | |
| MADRS change | 0.052 | 0.039 | | 0.025 | 0.153 | |
| Gender | | | | 0.013 | 0.302 | |
| Age | 0.008 | 0.428 | | 0.030 | 0.117 | |

* Model 2: Including both BDNFrs61888800 GG/T-carriers and NRG1 rs6994992 CC/T-carriers