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Brief report

No association between the serotonin transporter gene polymorphism 5-HTTLPR and cyclothymic temperament as measured by TEMPS-A

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ABSTRACT

Background: Temperaments are stable personality traits that can be considered subsyndromal risk factors of psychiatric illnesses. The 5-HTTLPR polymorphism of the serotonin transporter gene has been found to be associated with affective temperaments, particularly the cyclothymic temperament, as measured with the Temperament Evaluation of Memphis, Pisa, Paris and San Diego—autoquestionnaire version (TEMPS-A). In this study we have attempted to replicate this finding in a population-based sample which is five times as large as the sample used in the original study.
Methods: The 21 items of the cyclothymic subscale of TEMPS-A was filled in by 691 individuals (404 females, 287 males, 18–40 years) randomly recruited from the general population. DNA was isolated from saliva, and the serotonin transporter polymorphism 5-HTTLPR was genotyped using the polymerase chain reaction and fragment analysis.
Results: No significant association was found between 5-HTTLPR genotype and TEMPS-A score, neither when analysing by an additive allelic model nor when the different genotypes and allelic dominance were examined. Furthermore, no association was observed after gender stratification, or when TEMPS-A was analysed as a dichotomous measure, using a cut-off of $\geq$11 positive item responses.
Limitations: Although being used in clinical settings, TEMPS-A has not been officially validated in Norway.
Conclusions: This study suggests that there is no association between the 5-HTTLPR polymorphism and cyclothymic temperament as measured by TEMPS-A.

1. Introduction

Temperament refers to personality traits of an individual that are regarded as innate, and thus generally persistent throughout life, in contrast to aspects of the personality that are acquired. It has been reported that the different affective temperaments, i.e. depressive, cyclothymic, hyperthymic, irritable and anxious temperament, can be considered subsyndromal manifestations of minor and major mood disorders, and that they often precede these disorders (Rihmer et al., 2010). Temperaments have long been considered to be determined by genetic factors (Bouchard, 1994), and elevated scores of dysthymic and cyclothymic temperaments have been found in first degree relatives of individuals with bipolar disorder (Maier et al., 1995). In the search for genes involved in shaping personality traits, the serotonin transporter gene (*SLC6A4*) is a strong candidate, since serotonin has been implicated in a range of traits related

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to personality and temperament (Carver and Miller, 2006), and the serotonin transporter is the main regulator of synaptic serotonin levels. The promoter region of *SLC6A4* contains an insertion/deletion polymorphism, 5-HTTLPR, and it has been demonstrated that its short (S) variant reduces the transcriptional efficiency of the gene, resulting in decreased serotonin transporter expression (Lesch et al., 1996). 5-HTTLPR has been implicated in a range of psychiatric disorders, including autism, obsessive compulsive disorder (OCD), depression and bipolar disorder (Barnett and Smoller, 2009; Bloch et al., 2008; Gonda et al., 2005; Huang and Santangelo, 2008) although some of these results are controversial (Risch et al., 2009). Recently the S allele of 5-HTTLPR was reported to be significantly associated with affective temperaments (Gonda et al., 2009b; Gonda et al., 2006), particularly the cyclothymic temperament, in 139 psychiatrically healthy Caucasian females (Gonda et al., 2009b; Gonda et al., 2006). The temperament of the participants was measured using the Temperament Evaluation of Memphis, Pisa, Paris and San Diego—autoquestionnaire version (TEMPS-A), a self-report questionnaire developed by Akiskal et al. (2005b).

In this study we attempted to replicate the previously reported association between the 5-HTTLPR S allele and cyclothymic temperament measured by TEMPS-A in a sample consisting of 691 Norwegian adults recruited from the general population. The sample is five times as large as the original sample, providing strong power to detect the effect size estimated from previous studies in both the total samples and after gender stratification.

2. Methods

2.1. Subjects

The sample consisted of 691 Caucasians born in Norway and of Norwegian ancestry, aged 18–40 years, who volunteered to participate as controls in a main on-going study on adult attention-deficit/hyperactivity disorder (ADHD). Participants were included in the study after responding to invitation letters sent by mail through a random recruitment strategy of individuals from all across Norway, as described by Halmoy et al. (2010). All participants provided written informed consent and filled in a self-report questionnaire including the 21 items of the TEMPS-A concerning cyclothymic temperament (Akiskal et al., 2005b) and questions concerning present and lifetime psychiatric illness. Among these participants, 385 have been examined in a previous study by our group (Landaas et al., 2010). The study was approved by the Norwegian Regional Medical Research Ethics Committee West IRB #3 (FWA00009490, IRB00001872).

2.2. Genotyping

DNA was extracted from saliva using the Oragene™ DNA Self-Collection Kit (DNA Genotek Inc., Ontario, Canada). Genotyping of the promoter polymorphism of the serotonin transporter gene, 5-HTTLPR, was performed as described in our previous study (Landaas et al.). The 5-HTTLPR was amplified by the polymerase chain reaction (PCR) and genotyped by fragment analysis on the ABI3100 (Applied Biosystems, Foster City, CA, USA) using fluorescently labelled reverse primers (Heils et al., 1996). The genotypes were automatically called using the GeneMapper software (Applied Biosystems), and subsequently manually inspected by at least one person. The total genotyping rate was 0.964 (667/691 samples), and the concordance rate was 1.00. Detailed protocols for amplifications and fragment analysis are available upon request.

2.3. Measures

All participants filled in the cyclothymic subscale of the self-report questionnaire TEMPS-A (Akiskal et al., 2005a). TEMPS-A is a measure of affective temperaments that was developed by Akiskal and Mallya (1987) based on concepts of a continuum between affective temperaments and mood disorders. The original version was in interview format (TEMPS-I), but later a self-rated autoquestionnaire (TEMPS-A) has evolved (Akiskal et al., 2005b). This questionnaire contains subscales and items formulated with basis in diagnostic criteria for the affective temperaments cyclothymic, dysthymic, irritable, hyperthymic and anxious. TEMPS-A has been validated for use in both healthy and psychiatrically ill individuals (Akiskal et al., 2005b; Akiskal et al., 2005c). All participants scored the 21 items making up the cyclothymic subscale of the TEMPS-A, as listed in Akiskal et al. (2005a). Analyses were performed using the scale both as a continuous and a dichotomous measure. For the continuous measure each question answered by “yes” scored one point. For the dichotomous measure, a positive score was defined as ≥ 11 points, as suggested in a special supplement issue of the Journal of Affective Disorders on TEMPS-A (Akiskal and Akiskal, 2005).

2.4. Statistical analyses

The clinical data and the distribution of the TEMPS-A scores were analysed by descriptive methods using χ^2 tables, *t* tests and ANOVA performed by the Statistical Package for Social Sciences version 15.0.1 (SPSS Inc, Chicago, Illinois). The genetic statistical analyses were performed with the PLINK software (Purcell et al., 2007) and SPSS, based on additive allelic, genotypic and dominant/recessive models. Gender specific models were also analysed since the original report (Gonda et al., 2006) only involved females. Genotype distributions for 5-HTTLPR were consistent with Hardy–Weinberg Equilibrium (HWE), $p \geq 0.05$. For nominal significance a 2-tailed level of $p < 0.05$ was chosen. All *p*-values are presented without correction for multiple testing.

Power calculations were performed using the genetic power calculator (http://pngu.mgh.harvard.edu/~purcell/gpc/cc2.html). From Gonda et al., it can be estimated that the S allele explains approximately 5.4% of the total variance of the TEMPS-A scale in their sample. Hence, assuming an additive allelic model and using a significance level of 0.05, our study power is larger than 99%. Due to the well known winner's curse, the likely effect is probably less than what was found in the original study. We estimated that we have >80% power if the total variance explained by the S allele is 1.2% in our sample of 691 individuals.