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The association between neuroticism and the serotonin transporter polymorphism depends on structural differences between personality measures

Anja Schmitz^{a,*}, Juergen Hennig^a, Yvonne Kuepper^a, Martin Reuter^b

^a Department of Psychology, University of Giessen, Otto-Behagel-Str. 10F, D-35394 Giessen, Germany

^b Department of Psychology, University of Bonn, Römerstr. 164, D-53117 Bonn, Germany

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Abstract

Over the last decade the relationship between the serotonin transporter polymorphism (5-HTTLPR) and anxiety related personality traits has been intensely investigated. Although there are some meta-analytic approaches, the question remains open *why* the results of these studies are inconsistent. One suggestion is, that structural differences between personality measures lead to this heterogeneity. Based on this assumption we investigated the relationship between the 5-HTTLPR and neuroticism (N) as measured by the EPQ-R and NEO-FFI as well as harm avoidance (HA) as measured by the TCI in a sample of $N = 410$ healthy Caucasians. There were significant main effects of the s-allele for the EPQ-R-N ($F = 6.98$; $df = 1$; $p = 0.009$) as well as for the NEO-FFI-N ($F = 4.08$; $df = 1$; $p = 0.044$), but not for HA. In order to detect which aspects of negative emotionality are essential for the association with the 5-HTTLPR, all items of the three scales were tested with respect to their relation to the 5-HTTLPR. The 12 items which were significantly associated with the 5-HTTLPR form a new scale with a high internal consistency ($\alpha = .84$). With respect to the item contents it can be summarized that especially the components of depression and stress sensitivity relate to the transporter polymorphism.

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Keywords: Neuroticism; Serotonin; 5-HTTLPR; EPQ-R; NEO-FFI; TCI; Negative emotionality

* Corresponding author. Tel.: +49 641 9926155; fax: +49 641 9926159.

E-mail address: anja.schmitz@psychol.uni-giessen.de (A. Schmitz).

1. Introduction

There is strong evidence that a great part of the variability in personality is explained by genes (up to 60%, for example Bouchard, Lykken, McGue, Segal, & Tellegen, 1990), yet the molecular genetic basis of personality remains widely unknown. The best starting point to investigate, which genetic factors influence personality traits are personality theories that propose a biological basis. Some personality theories relate the activity of distinct neurotransmitter systems to distinct personality traits (e.g. Cloninger, 1987) thereby suggesting potential candidate genes to be investigated. Especially gene loci on candidate genes with known functional effects on neurotransmitter pathways can be investigated with respect to their associations to personality traits.

In this field of research the serotonergic system is of special interest. Both personality and psychopathological diseases are supposed to be associated with differences in the activity of serotonergic pathways. Serotonin (5-HT) plays a major role in depression and anxiety disorders (e.g. Bell & Nutt, 1998; Deakin & Graeff, 1991) and the modulation of the 5-HT system is crucial for their therapy. For example, selective serotonin re-uptake inhibitors (SSRIs) are highly effective antidepressants (Steffens, Krishnan, & Helms, 1997). Furthermore, the 5-HT system was also linked to anxiety-related personality traits. Cloninger (1987) for example proposed 5-HT to play a decisive role in harm avoidance (HA). In the same line Gray (1970) related the behavioral inhibition system (BIS) to serotonergic pathways. Thus this neurotransmitter system is especially suitable to be investigated with respect to the relationship between personality, psychiatric disorders and their underlying neurotransmitter functioning.

In their pioneer work Lesch et al. (1996) were able to demonstrate a significant association between the 5-HTTLPR polymorphism and anxiety-related personality traits, namely neuroticism, harm avoidance and the anxiety factor of Cattell's 16PF questionnaire. The 5-HTTLPR is a 44-bp insertion/deletion polymorphism in the promotor region of the serotonin transporter (5-HTT) gene. The shorter (s) allele of 5-HTTLPR was associated with reduced 5-HTT gene transcription rate leading to reduced 5-HTT binding sites and reduced 5-HT reuptake (Heils et al., 1996; Lesch et al., 1996). In the study of Lesch et al. the s-allele was identified as the dominant allele, implying that the presence of at least one short allele (genotypes ss or sl) is associated with significantly higher scores in personality traits of negative emotionality.

Since the first stimulating findings of Lesch et al. (1996) many attempts to replicate these results followed. While some studies support the association between the s-allele and neuroticism (e.g. Greenberg et al., 2000), or HA (e.g. Ricketts et al., 1998), other studies did not (e.g. Lang et al., 2004).

The first systematic approach to summarize the outcomes of these heterogeneous results in a meta-analysis found little evidence for an association between the 5-HTTLPR polymorphism and any anxiety-related personality trait (Munafo et al., 2003). However, the following attempts by Sen, Burmeister, and Ghosh (2004) and by Schinka, Musch, and Robichaux-Keene (2004) identified a significant main effect of the s-allele of the 5-HTTLPR on neuroticism but not on HA. Recently, in a fourth meta-analysis, Munafo, Clark, and Flint (2005a) included all studies with nonclinical samples that were previously taken into consideration plus two new available studies on this issue. Surprisingly, this most thorough investigation led to the opposite result: only the homozygous short ss genotype of the 5-HTTLPR polymorphism was associated with higher

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