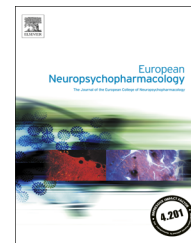




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Therapygenetics: 5-HTTLPR genotype predicts the response to exposure therapy for agoraphobia

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Abstract

This study was intended to assess the extent to which the low-expression allele of the serotonin transporter gene promoter predicts better response to exposure-based behavior therapy in patients with panic disorder with agoraphobia (PDA). Ninety-nine patients with PDA underwent a 1-week in vivo exposure-based behavior therapy program and provided saliva samples to extract genomic DNA and classify individuals according to four allelic forms (S_A , S_G , L_A , L_G) of the 5-HTT-linked polymorphic region (5-HTTLPR). We determined whether the 5-HTTLPR genotype predicted change in avoidance behavior in PDA following treatment. After controlling for pre-treatment avoidance behavior, the 5-HTTLPR low-expression genotypes showed a more favorable response to exposure therapy two weeks following treatment, compared to the other patients. This study suggests a genetic contribution to treatment outcome following behavior therapy and implicates the serotonergic system in response to exposure-based treatments in PDA.

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1. Introduction

The serotonin transporter length polymorphism (5-HTTLPR) has received considerable attention over the last few years in the study of gene-environment (GxE) interactions in

emotional disorders. Many studies, including meta-analyses, reported an interaction with a variety of environmental factors while others failed to find such a relationship (Colasanti et al., 2011; Feinn et al., 2005; Karg et al., 2011; Minelli et al., 2011; Pergamin-Hight et al., 2012; Schinka, 2005; Schinka et al., 2004; Serretti et al., 2006).

An explanation for this apparent contradiction has been proposed, in that an interaction effect between the 5-HTTLPR and the environment is not of a general nature

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but is restricted to some specific environmental factors (Blaya et al., 2007; Minelli et al., 2011; Munafo et al., 2008).

Stein et al. (2008) found in young adults a statistically significant interaction between 5-HTTLPR genotype and levels of childhood (emotional or physical) maltreatment. Specifically, SS individuals with higher levels of maltreatment had significantly higher levels of anxiety sensitivity. Klauke et al. (2011) showed a GxE effect of more active 5-HTT genotypes and childhood maltreatment on anxiety sensitivity. These two studies provide evidence of a genetic influence on anxiety sensitivity and this effect is modified by severity of childhood maltreatment. Further, it has also been demonstrated that 5-HTTLPR SS-homozygotes who experienced 2 or more separation life events showed a significantly higher prevalence of panic disorder compared to those with SL-heterozygotes or LL-homozygotes. Also, 5-HTTLPR SS-homozygotes who experienced more separation life events showed a significantly higher harm avoidance (Choe et al., 2013). Together, these findings are consistent with the notion that 5-HTTLPR operates broadly to moderate emotional response to stress. The issues of replication and specificity also apply to the study of the effect of 5-HTTLPR genotype on the therapy response in psychiatric disorders.

Considerable effort is invested in elucidating the genetic factors that determine and can predict the effects of pharmacological therapy for psychiatric disorders (Arias et al., 2003; Keers and Aitchison, 2011; Kim et al., 2006; Perna et al., 2005; Serretti et al., 2006; Taylor et al., 2010; Zanardi et al., 2001). Equally important but much less studied is the influence of genetic variation on the efficacy of psychological therapy. It is both of theoretical and clinical interest to identify biological markers for individualization of cognitive behavior therapy (CBT) associated with successful outcome. These studies may give us a more nuanced understanding of psychopathology, which in turn can enhance the ability to tailor treatments individually based on genetic profile, thereby increasing the effectiveness of psychological treatments. This way, 'therapygenetics', similar to pharmacogenetics (Keers and Aitchison, 2011), may have the potential to determine who is more likely to respond to which form of treatment (e.g. CBT, drugs or both).

Currently, there is a lack of studies investigating the role of genetic variants in the efficacy of CBT in panic disorder with agoraphobia (PDA). Traditionally, CBT was considered to exert its effect via psychosocial mechanisms in contrast with pharmacological treatment, which was considered to act via biological mechanisms. However, research has clearly shown that the changes in affect, behavior and cognition seen after CBT have biological underpinnings and are accompanied by significant and disorder specific changes in brain metabolism (Goossens et al., 2007; Linden, 2006; Roffman et al., 2005).

The genetic contribution to the liability of PDA is around 30-40% (Hettrema 2001). In the case of anxiety disorders, several studies have suggested a genetic contribution to treatment outcome following CBT (Bryant et al., 2010; Eley et al., 2012; Hudson et al., 2013; Kim et al., 2006; Lester et al., 2012; Lonsdorf et al., 2010; Reif et al., 2014). The study of Bryant et al. (2010), in patients with posttraumatic stress disorder (PTSD), showed that six months after treatment, the 5-HTTLPR low-expression genotype group (S or L_G allele carriers) still displayed more severe

PTSD-symptoms relative to the other patients. Eley et al. (2012) found that the type of 5-HTTLPR predicted response to CBT among children with anxiety disorders. Specially, children with two copies of the low-expressing S-allele had better symptomatic response to treatment at follow-up (i.e., 6 months after completion of CBT) than children with one or two copies of the L-allele. Lonsdorf et al. (2010) demonstrated that panic disorder patients with the COMT-val158met/met genotype might profit less from (exposure-based) CBT treatment methods as compared to patients carrying at least one val- allele. In this study, no association was found with the 5-HTTLPR/rs25531 genotypes. Kim et al. (2006) showed that the BDNF Val66Met genotype predicts response to cognitive behavior therapy in PTSD. Focusing on neurotrophic genes, Lester et al. (2012) demonstrated in a sample of 374 anxiety-disordered children, that children with one or more copies of the T allele of nerve growth factor (NGF rs6330) were significantly more likely to be free of their primary anxiety diagnosis at follow-up. No significant associations were observed between brain-derived neurotrophic factor (BDNF rs6265) and response to psychological therapy. The same group followed up on these findings, this time using a 'risk index' approach combining demographic and clinical data with genetic data (5HTTLPR and NGF rs6330) to predict outcome of CBT in a group of anxious children. Results showed that children scoring high on this index were considerably more likely to retain their primary anxiety disorder at follow-up (Hudson et al., 2013). In a very recent paper, Reif et al. (2014) report on the impact of MAOA-uVNTR on therapy response, behavioral avoidance and brain activity during fear conditioning in a study on CBT in PDA. The results showed that patients with the long MAOA risk alleles (causing higher activity of MAO- A) profit less from exposure-based CBT as reflected by lower response rates. During exposure to a standardized behavior avoidance test, high-risk patients also reported higher anxiety, more panic attacks and elevated heart rate. Furthermore, fMRI scanning during a classical fear-conditioning paradigm in a subset of these patients (n=42) demonstrated that patients carrying the protective allele showed increased activation of the anterior cingulate cortex (ACC) upon presentation of the CS + during acquisition of fear. Such activation was absent in high-risk allele carriers.

In line with our previous work on the role of the serotonin system in PDA (Colasanti et al., 2011; Kim et al., 2006; Schruers and Griez, 2003, 2004; Schruers et al., 2000; Schruers et al., 2002) and more specifically of the 5-HTTLPR (Schruers et al., 2011), we focused on the role of the 5-HTTLPR.

In the present study, we investigated the effect of variation in the 5-HTTLPR gene on the efficacy of a one-week intensive exposure-based therapy for agoraphobia in a sample of patients with PDA. In line with the study of Eley et al. (2012), we hypothesized that the S-allele would be associated with enhanced response to therapy.

2. Materials and methods

2.1. Participants

Ninety-nine patients of white European heritage who completed the 1-week in vivo exposure-based behavior therapy

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