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The role of the serotonin transporter polymorphism for the endocrine stress response in newborns

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Summary A functional polymorphism in the 5′flanking region of the serotonin transporter gene (17q11.2, 5-HTTLPR) alters the transcription of the 5-HT transporter gene and seems to be associated with depression and anxiety-related personality traits in humans. This effect appears to be the most pronounced in individuals who are homozygous for the low-expressing "*S*" allele who have experienced significant critical life events in the past. Animal studies now link this polymorphism to an increased stress reactivity of the hypothalamus—pituitary—adrenal (HPA) axis. In humans, it remains unknown whether this polymorphism by itself affects HPA axis or only in interaction with environmental factors. The aim of the present study was to investigate the role of the 5-HTTLPR polymorphism for the HPA axis in humans early in the development at a time when individuals were exposed to very few or no early adverse experiences so far.

We genotyped DNA for the 5-HTTLPR polymorphism including the A/G single-nucleotide polymorphism (SNP) in 126 three-day old newborns. The newborn's stress response was stimulated by a heel prick which is a part of a routine medical procedure. The heel prick induced a significant biological (i.e., cortisol) stress response in all newborns. Newborns with the "*S*/*S*" genotype showed a significantly higher endocrine response in comparison to newborns with "*L*/*L*" or "*S*/*L*" genotype.

In this sample of newborn babies, the 5-HTTLPR genotype affected the HPA stress response to painful stimulation irrespective of additional influence of pre- or perinatal environmental factors we measured.
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1. Introduction

An increasing number of studies links genetic variations with psychiatric disorders. Besides, the meaningful variation in DNA sequences for instance single-nucleotide polymorphism

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(SNP) may alter mRNA stability or the amino acid sequence which then can then result in a modified gene product. Allele variants in regulatory regions however, may alter transcription factor binding or act via further regulatory mechanisms which may result in a changed quantity of expressed gene products. These polymorphisms appear to have a significant impact on neurotransmitter systems in the brain which can have significant consequences for cognitive or emotional processing as well as psychopathology. Among the most frequently studied neurotransmitter systems with respect to emotional and behavioral endophenotype differences is the brain serotonin system. It is pivotally involved in emotional processes, and dysregulation of the serotonergic system has been described in several psychopathological disorders such as depression (review in Jans et al., 2007), social anxiety disorder (Mathew and Ho, 2006), posttraumatic stress disorder (Vieweg et al., 2006), or obsessive–compulsive disorder (Ninan, 2003).

A functional polymorphism (5-HTTLPR) in the 5′flanking region of the serotonin transporter gene (5-HTT, 17q11.2) alters gene transcription of the serotonin transporter and seems to be associated with depression as well as with anxiety-related personality traits in humans (Caspi et al., 2003; Hariri et al., 2005; Lesch et al., 1996; Sen et al., 2004). Likewise, an association of this polymorphism with variations in the endocrine stress reactivity of the hypothalamus–pituitary–adrenal (HPA) axis was described in animals (Barr et al., 2004a,b). Effective antidepressant and anxiolytic drugs targeting the serotonin transporter underline the importance of this polymorphism in the etiology of psychopathological disorders.

5-HTTLPR, in particular the serotonin transporter-linked polymorphic region, is a 44 bp insertion/deletion polymorphism that consists of two alleles in the transcriptional control region of the 5-HTT gene: the 'short' ("*S*") allele comprising 14 copies of a 20–23 bp irregular repeat unit and the 'long' ("*L*") allele comprising 16 copies. The transcriptional activity of the "*L*" allele is about two times higher than that of the "*S*" allele (Heils et al., 1996). Additionally, the "*S*" allele is associated with significantly reduced 5-HTT binding in limbic brain regions, a lower 5-HTT expression and decreased serotonin reuptake into the presynaptic neuron (Lesch et al., 1996). In addition to the "*S*" and "*L*" alleles, there is an A>G SNP within the repetitive region that comprises the 5-HTTLPR (dbSNP: rs25531), such that it is only present on the "*L*" allele. As with the loss-of-function *S* allele, the derived "L_G" allele results in decreased 5-HTT transcription relative to the "L_A" allele (Hu et al., 2005; Wendland et al., 2006). 5-HTTLPR genotype frequencies vary across different populations although rare alleles contain up to 20 copies of the repeat sequence. In European populations the frequency is ~40% for the "*L*" allele and ~60% for the "*S*" allele, respectively (Gelernter et al., 1997).

Although genes determine inter-individual differences in many pathological diseases to some extent, an increasing number of studies suggest that environmental factors and especially gene–environment interactions play a pivotal role in the etiology of psychopathology (Caspi et al., 2003; Kendler et al., 2005; Neumeister et al., 2002). Considering genetically determined variation in the serotonergic system, increasingly strong data from human and animal studies show the importance of environmental factors for the association between 5-HTTLPR and psychopathology. A relative reduction of 5-HTT gene transcription is linked with an increased risk for psychopathology in association with the early adverse (Caspi et al., 2003; Hariri et al., 2006; Kendler et al., 2005; Neumeister et al., 2002). Caspi et al. (2003) described that individuals with at least one *S* allele of the 5-HTTLPR and early adverse experience (e.g., childhood abuse) showed an increased risk for major depression or suicidal ideation. In contrast, individuals with "*L*/*L*" genotype were not at greater risk for depression irrespective of the number of experienced critical life events (Caspi et al., 2003). Additionally, Ansorge et al. (2004) revealed that genetic polymorphisms that reduce 5-HTT expression might impact on the early development of the central nervous system (CNS) which subsequently can modify emotional responses to stress (Ansorge et al., 2004). Thus, individuals with the "*S*" allele seem to be vulnerable to develop depression when exposed to a number of critical life events. While other groups replicated these findings (Bennett et al., 2002; Eley et al., 2004; Kendler et al., 2005; Neumeister et al., 2002), conflicting results also exist (Gillespie et al., 2005; Ohara et al., 1998; Surtees et al., 2006).

The hypothalamus–pituitary–adrenal (HPA) axis might be an important mediator of the association between the 5-HTTLPR and psychopathology as alterations of the HPA axis are linked to psychopathology, e.g., depression or anxiety disorders (Chrousos, 2000; McEwen, 2005; Selye, 1936). Although the causal relation between HPA axis alterations and psychopathology remains unclear, it might be hypothesized that individual differences in HPA axis activity influence the individual's vulnerability for psychopathology (Dallman et al., 1987; Fries et al., 2005). The HPA axis is activated in response to a multitude of stimuli. Corticotropin-releasing hormone (CRH) is released from neurons in the paraventricular nucleus (PVN) of the hypothalamus stimulating the secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary. Subsequently, ACTH reaches the adrenal glands stimulating the synthesis and release of species-specific glucocorticoids. Glucocorticoids influence metabolic and immune processes, adapting the organism to changing demands and promoting organism's survival (Chrousos, 2000; Chrousos and Gold, 1992; Kirschbaum and Hellhammer, 1989).

As HPA axis activity is under partial control of the serotonergic system (Fuller, 1996; Lowry, 2002), this axis might be influenced by the 5-HTTLPR polymorphism. In a study with rhesus macaques, Barr et al. (2004b) showed an association between the "*S*" allele of the polymorphism and dysregulation of HPA axis functioning with early environmental conditions influencing this association. Rhesus macaques with at least one "*S*" allele of an analogous serotonin transporter polymorphism (rh5-HTTLPR) demonstrated an increased secretion of ACTH in response to stress when they experienced adverse rearing conditions during childhood. Conversely, rhesus macaques with at least one "*S*" allele and without critical rearing conditions showed a normal ACTH response to separation stress (Barr et al., 2004b). The study of Barr et al. (2004b) underscored the importance of environmental factors for the association between 5-HTTLPR genotype and HPA axis functioning. However, there is only one study showing a main effect of the 5-HTTLPR genotype on HPA axis parameters so far (Gotlib et al., 2008) and one study

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