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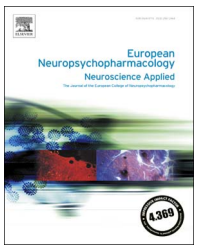

The effect of 5-HTTLPR and a serotonergic multi-marker score on amygdala, prefrontal and anterior cingulate cortex reactivity and habituation in a large, healthy fMRI cohort

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Abstract
Major depressive disorder (MDD) is characterized by low mood for at least two weeks. Impaired emotion regulation has been suggested to be the consequence of dysfunctional serotonergic regulation of limbic and prefrontal regions, especially the amygdala, the anterior cingulate cortex (ACC) and the prefrontal cortex (PFC). The impact of genetic variation on brain function can be investigated with intermediate phenotypes. A suggested intermediate phenotype of MDD is emotion recognition: The *5-HTT*LPR polymorphism of *SLC6A4* as well as other serotonergic genes have been associated with amygdala and prefrontal function during emotion recognition.

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Polygenic;
Serotonin;
Habituation

Previously, it has been suggested that habituation is a more reliable index of emotion recognition than functional activation. We examined the relationship of genes involved in serotonergic signaling with amygdala as well as prefrontal functional activation and habituation during an emotion recognition task in 171 healthy subjects. While effects of *5-HTT*LPR and of a serotonergic multi-marker score (*5-HTT*LPR, *TPH1(rs1800532)*, *TPH2(rs4570625)*, *HTR1A (rs6295)* and *HTR2A(rs6311)*) on amygdala activation did not withstand correction for multiple regions of interest, we observed a strong correlation of the multi-marker score and habituation in the amygdala, DLPFC, and ACC. We replicated a well-studied intermediate phenotype for association with *5-HTT*LPR and provided additional evidence for polygenic involvement. Furthermore, we showed that task habituation may be influenced by genetic variation in serotonergic signaling, particularly by a serotonergic multi-marker score. We provided preliminary evidence that PFC activation is an important intermediate phenotype of MDD. Future studies are needed to corroborate the results in larger samples.

1. Introduction

Major depressive disorder (MDD) is a psychiatric disease, characterized by negative mood plus other required symptoms over a period of at least two weeks. Mood in MDD is associated with negatively biased emotional processing: Emotional stimuli arouse patients with MDD more than they do in healthy subjects. This susceptibility to negative emotional stimuli has been suggested to underlie impaired mood regulation (Mathews and MacLeod, 2005), eventually resulting in symptoms of MDD such as low mood. Lesion, electrophysiological and neuroimaging studies imply an imbalance between prefrontal cortex (PFC), anterior cingulate cortex (ACC) and amygdala function in patients with MDD, which has been suggested as a neural correlate of biased emotional processing (Davidson and Irwin, 1999; Disner et al., 2011; Koenigs and Grafman, 2009).

Although MDD is a partially heritable disorder with 46% concordance in monozygotic twins (Lohoff, 2010; McGuffin et al., 1996), genome-wide association studies did not explicitly identify serotonergic polymorphisms (Levinson et al., 2014; Ripke et al., 2013), while they recently discovered polymorphisms involved in tissue development, neurogenesis and most recently, targets of antidepressant medications (Howard et al., 2017; Hyde et al., 2016; Wray and Sullivan, 2017). The antidepressant effect of serotonin reuptake inhibitors (SSRIs) supported the theory of imbalanced serotonergic neurotransmission in MDD and led to the extensive study of genes coding for proteins involved in serotonin (5-HT) signaling. These include: (1) Serotonin-transporter-linked polymorphic region (*5-HTT*LPR) (Lesch et al., 1996), a variable number of tandem repeats (VNTR) in the promoter region of the *solute carrier family 6 member 4* gene (*SLC6A4)* – which codes for the serotonin re-uptake transporter (SERT) – (2) single nucleotide polymorphisms (SNPs) in genes coding for tryptophan hydroxylases (TPH), which are rate limiting enzymes in the synthesis of serotonin (Canli et al., 2005; Chen et al., 2008; Lee et al., 2009), and (3) SNPs in genes coding for serotonin receptors (HTR) (Czesak et al., 2006; Fisher et al., 2009; Khait et al., 2004; Lee and Ham, 2008).

Effects of serotonergic polymorphisms on emotion regulation were shown to be present in a particular brain network. The core of this emotional network proposed by previous studies is the amygdala, which is responsible for emotional assessment, fear learning and detection of threat (Lonsdorf et al., 2011). The amygdala is interconnected with a widespread network of cortical and subcortical areas. The strongest connections with the amygdala can be found in the medial PFC, particularly the ACC; further connections include the orbital PFC, the dorsolateral PFC (DLPFC), the hippocampus and the posterior cingulate cortex (Price and Drevets, 2010). Top-down regulation of the amygdala is one key function of the PFC, especially in its medial and dorsolateral part. In MDD, imbalances of amygdala and prefrontal areas have been consistently observed, showing increased functional activation of the amygdala and decreased functional activation in the DLPFC in response to emotional stimuli (Disner et al., 2011; Fakhoury, 2015; Murray et al., 2011). Further, studies suggested that the DLPFC is part of a regulatory system and can modulate the amygdala in case of an avoidance response (Ochsner et al., 2012). The aforementioned network is targeted by serotonergic projections from the raphe nuclei (Yildirim and Derksen, 2013). We therefore hypothesized that serotonergic polymorphisms effect activation and habituation of limbic and prefrontal regions, including amygdala, ACC and the DLPFC.

Given the phenotypic and diagnostic heterogeneity of MDD, imaging genetics studies aim to identify intermediate neuroimaging phenotypes that are more directly associated with genetic risk variants than behavioral features (Meyer-Lindenberg and Weinberger, 2006). In 2002, Hariri et al. reported that carriers of the *5-HTT*LPR S allele (lower 5-HT expression) showed increased amygdala functional activation compared to L-allele carriers (higher 5-HT expression) in an emotional face matching task (Hariri et al., 2002a, 2002b). However, monogenic effects repeatedly failed to achieve significance and the effect of the *5-HTT*LPR remains controversial (Bastiaansen et al., 2014; Murphy et al., 2013). Additionally, a recently discovered SNP in proximity of the *5-HTT*LPR influences the expression of serotonin: rs25531 G-allele carriers who

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