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Research report

Effect of 5-HTTLPR on current source density, connectivity, and topological properties of resting state EEG networks

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ABSTRACT

The S allele of serotonin transporter gene (5-HTTLPR) has been found to increase the risk of depression and other mental health problems, but some evidence suggests that S-allele carriers outperform subjects carrying the long allele in an array of cognitive tasks. Evidence linking this polymorphism with individual variation in electrophysiological properties of resting state brain networks is very limited. This study investigated the effect of 5-HTTLPR polymorphism on EEG current source density, connectivity, and topological properties of resting state networks. We collected genetic and resting state EEG data in 113 Caucasians. As compared to L-homozygotes, S-allele carriers showed lower current source density and connectivity in most frequency bands in areas overlapping with the default mode and emotion regulation regions. The analysis of graph-theoretical measures showed that S-allele carriers, as compared to L-homozygotes, have less optimal topological properties of brain networks in theta, but more optimal in alpha band. This dissociation may reflect the predisposition to emotional disorders, which is inherent to S-allele carriers, and, on the other hand, their superior functioning in some cognitive domains.

The serotonin transporter (5-HTT) is one of the most widely investigated genetic markers of individual variation in serotonin-ergic function. It regulates the strength and duration of serotonin influence on postsynaptic receptors by its reuptake from a synaptic cleft (Blakely et al., 1994). Human's 5-HTT is coded by SLC6A4 gene, which is localized on the 17-th chromosome (Gelernter et al., 1995). The promoter region of the serotonin transporter gene (5-HTTLPR) contains short (S) and long (L) variants. The S one is associated with the reduced transcriptional efficiency (Lesch et al., 1996). In addition, the long allele contains A/G single nucleotide polymorphism with the LG allele being functionally similar to the S allele (Hu et al., 2005). The 5-HTTLPR polymorphism determines the 5-HTT gene expression and is considered to contribute to many neuropsychiatric disorders, including suicidal behavior (Arango et al., 2003) and depression (Lesch et al., 1997).

The S allele has been found to increase the risk of depression in individuals previously exposed to stressful life events (Caspi et al., 2003). Subsequently, some researchers did not replicate this finding (e.g., Chipman et al., 2007). A number of *meta*-analyses were conducted and found no evidence supporting the presence of the interaction between 5-HTTLPR and stress in predicting depression (e.g., Munafò et al., 2009; Risch et al., 2009). However, slight, but statistically significant effect was found in later *meta*-analyses (e.g., Clarke et al., 2010; Sharpley et al., 2014). The 5-HTTLPR S allele is not associated with only negative outcomes. Some evidence suggests that S-allele carriers outperform subjects carrying the long allele in an array of cognitive tasks (for a review see Homberg and Lesch, 2011). They show the higher scores on a divergent thinking (Volf et al., 2009), better attention to differences in the probability of winning and better visual planning (Roiser et al., 2006), more intense error processing (Althaus et al., 2009), superior performance in Wisconsin Card Sorting Test (Borg et al., 2009), and higher IQ scores (Volf et al., 2015c). This is in line with the 'differential susceptibility' hypothesis, which suggests that most susceptible to adversity 'risk alleles' may benefit from the absence of adversity (Belsky et al., 2009). Such framework implies that the 'risk alleles' may have a higher sensitivity to environmental challenges, which is detrimental in some circumstances, but beneficial in others. Indeed, S-allele carriers demonstrate the heightened amygdala response to a negative emotional stimuli (Hariri et al., 2002; Munafò et al., 2009; Schinka et al., 2004; Sen et al., 2004; Thomason et al., 2010), which is in line with the notion that even in a resting state, S-allele carriers show an increased

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cerebral blood flow in the amygdala and a decreased flow in the ventromedial prefrontal cortex (Rao et al., 2007). The enhanced basal metabolism in the fronto-limbic structures is associated with an increased probability of developing anxiety-depression spectrum disorders in S-allele homozygotes (Graff-Guerrero et al., 2005). In addition, S-allele carriers, as compared to L-allele homozygotes, show stronger influence of the long-term stress exposure on the structure and activity of frontal brain regions (Canli et al., 2006; Selvaraj et al., 2011). Several studies demonstrated a link between the S allele and the difficulty to disengage from the processing of emotional stimuli (Beevers et al., 2009, 2010; Gilman et al., 2015). Dannlowski et al. (2007) showed that in clinically depressed patients, the genetic susceptibility for major depression (i.e., the presence of the S allele) is realized via dysfunctional neural activity during the emotion processing.

Several studies suggest that 5-HTT gene variation has an effect on the connectivity among key areas involved in emotion regulation, such as amygdala, prefrontal cortex (PFC), anterior cingulate, and insula (Dannlowski et al., 2010; Hariri et al., 2002; Ma et al., 2014). This is particularly the case for the circuitry linking the amygdala with regions of the prefrontal cortex (Holmes, 2008; Pezawas et al., 2005). Growing evidence links the S allele with reduced PFC-amygdala connectivity (Beevers et al., 2010; Gillihan et al., 2011; Heinz et al., 2005; Pezawas et al., 2005), which suggests that individuals with at least one S allele may have difficulty down-regulating heightened emotional responses. Wiggins and colleges (2012) showed that children and adolescents with S/S genotype have the weakest connectivity between the posterior hub and superior medial frontal cortex in the default network compared to other 5-HTTLPR genotypes, but this connectivity strengthens with age.

The majority of studies in this area have used functional magnetic resonance imaging (fMRI). Although this method is well suited for the study of human brain function, electroencephalography (EEG) remains an important tool, which has several advantages compared to fMRI. While fMRI is based on blood-oxygenation-level-dependent (BOLD) signal registration, which is an indirect measure of neural activity, EEG can provide more direct information about neuronal events. Moreover, EEG has high temporal resolution, which is much closer to the dynamics of cognitive processes in the brain than the temporal resolution of fMRI method. Recent findings imply that oscillatory processes in the EEG frequency range can take a significant part in the functional integration of different brain regions (Buzsaki and Draguhn, 2004) and different frequency oscillations may be connected with different functional processes (Nunez, 2000). However, this method has serious limitations, which are inherent in the nature of EEG data. Because EEG is registered on the scalp, activity of cortical sources could only be deduced by means of source localization methods, which generally have low spatial resolution (Schoffelen and Gross, 2009).

Investigations of EEG recordings from twins have revealed significant genetic effects on EEG power spectrum (Christian et al., 1996; McGuire and Troisi, 1998; van Beijsterveldt and van Baal, 2002) and connectivity between different cortical regions as measured by coherence (van Beijsterveldt et al., 1998). However, studies investigating the association of 5-HTTLPR genotype with resting-state EEG characteristics are very rare.

Lee et al. (2011) explored the modulatory effect of 5-HTTLPR polymorphism on channel-level EEG activity in eyes-closed resting state in a Chinese sample. Consistent global trend linking L-allele carriers, as compared to non-carriers, with a higher regional power regardless of frequency band has been revealed. Volf and colleagues analyzed the effect of 5-HTTLPR polymorphism on channel- and source-level EEG activity in the eyes-closed resting condition in a Caucasian sample. The most pronounced difference was found between S/S and S/L genotype carriers, with this effect being moderated by sex and age (Volf et al., 2015a,b, 2016). A number of studies explored the association of 5-HTTLPR polymorphism with frontal EEG asymmetry both in the rest and in task condition. Thus, a small effect of S-allele carrying on resting state prefrontal EEG alpha asymmetry has been noted by Bismark et al. (2010) and was interpreted as a result of the interaction with lifetime major depression disorder. Papousek et al. (2013) noted a clear shift of the dorsolateral frontal activity to the right while viewing a film containing traumatic content in S, but not in L-homozygotes. They connected it with a tendency to withdrawal-oriented response to the negative emotion cues (Papousek et al., 2013).

Apart from one study (Volf et al., 2016), all above-mentioned studies employed channel-level EEG measures, which diminishes the possibility to link the observed effects with specific cortical areas. Besides, to the best of our knowledge, no study to date investigated the effect of 5-HTTLPR polymorphism on EEG connectivity measures. This is unfortunate, because EEG, given its high temporal resolution, may provide an information about interregional communication, which is more plausible than that provided by fMRI connectivity measures. It seems quite probable that inter-allele differences would be more evident in the organization of electrophysiological brain networks than in overall measures of oscillatory activity. Moreover, these differences may be more specifically associated with changes in topological organization of brain networks rather than in general decrease or increase of connectivity strength. Graph theoretical approaches allow to model the brain as a complex network represented by vertices (i.e., brain regions) and edges (i.e., functional connections) (Bullmore and Sporns, 2009; Rubinov and Sporns, 2010). Many studies have demonstrated that the brain is organized as a highly efficient network, generally referred to as a small-world network (Stam, 2004; Hagmann et al., 2007; Watts and Strogatz, 1998). Small-world networks are characterized by relatively high level of local clustering and a limited number of random long-range connections. Such architecture enables the information transfer with high efficiency at a low wiring cost (Salvador et al., 2005; Achard and Bullmore, 2007; He et al., 2007, 2009; Chen et al., 2008; Hagmann et al., 2008; Gong et al., 2009). "Small-worldness", a measure, which allows to quantify the degree of correspondence between network organization and prototypical small-world architecture, is commonly seen as a measure of optimal efficiency in network configuration. The small-world networks enable higher rates of information processing and learning (Simard et al., 2005). Cognitive decline associated with pathological and physiological aging is associated with decreased small-world properties and increased randomness of functional networks derived from resting- and active-state fMRI connectivity patterns (Achard and Bullmore, 2007; Gong et al., 2009; Stam et al., 2006; Wang et al., 2010; Wu et al., 2013). Similar effects were also shown for connectivity patterns derived from EEG data (van Gaal et al., 2012; Knyazev et al., 2015; Smith et al., 2010).

In this study, we aimed to explore the effect of 5-HTTLPR polymorphism on the source-level EEG activity in both eyes-closed and eyes-open resting condition. Additionally, we aimed to perform source-level connectivity analysis and explore the effect of 5-HTTLPR polymorphism on topological properties of the global resting-state EEG network. Given the paucity and inconsistency of the existing EEG evidence, this is largely exploratory study. However, taking into account the existing evidence of the vulnerability, which is inherent to S-allele carriers, we expected that this would be somehow reflected in the less efficient organization of their electrophysiological networks.