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Interactive effect of 5-HTTLPR genotype and age on sources of cortical rhythms in healthy women

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ABSTRACT

This study was aimed to localize the effects of 5-HTTLPR (serotonin-transporter-linked polymorphic region) on the age differences of spontaneous EEG activity in women using neuroimaging analysis sLORETA (Standardized Low Resolution brain Electromagnetic Tomography). DNA samples extracted from cheek swabs and resting-state EEG recorded at 60 standard leads were collected from young (YW, $N = 86$, 18–35 years) and older (OW, $N = 45$; 55–80 years) healthy women. We have shown that advanced age was associated with increased posterior EEG desynchronization in S′/S′. S′ (LG allele was grouped with S alleles owing to its functional equivalence and this group was labeled as S′) genotype carriers denoted by decrease of delta – beta1 current source density, and to a lesser extent in L/L homozygotes denoted by decrease in delta activity. In heterozygotes OW, as compared with heterozygotes YW, higher source density estimates of beta1 in frontal and temporal cortex were observed. Age differences were more pronounced in the right hemisphere in S′/S′ and L/L carriers and in the left hemisphere in heterozygotes. We also found that in OW, current source density estimates of theta, alpha1, alpha2, alpha3 and beta1 sources in the right occipital lobe were higher in S′/L than in S′/S′ carriers. These results may have implications for understanding 5-HTT-dependent variation in the effect of aging on brain activity.

1. Introduction

A candidate gene is a gene whose variation is suspected of being associated with a specific brain, behavioral or clinical features. Serotonergic neurons have an extensive network of connections with huge number of cortical areas. So genes involved in the regulation of serotonergic neurotransmission are candidate genes that might be associated with characteristics of resting state EEG activity. The serotonin transporter (5-HTT) removes serotonin from the synaptic cleft and mediates the magnitude and duration of 5-HT signaling (Blakely et al., 1994). The human 5-HTT is encoded by the serotonin transporter gene (SLC6A4) on chromosome 17q12 (Gelernter et al., 1995). The 5-HTT gene promoter includes a polymorphism with short (S) and long (L) repeats in a 5-HTT-linked polymorphic region (5-HTTLPR) (Lesch et al., 1996). The S allele is associated with decreases in mRNA level, protein density and 5-HT reuptake compared with the L allele. Recently it has been discovered that the long 5-HTTLPR allele has two variants (LA and LG) with the latter one found to be functionally similar to the S allele. Thus, only the LA variant is high expressing allele of the serotonin transporter gene 5-HTTLPR (Hu et al., 2005).

A great number of previous investigations have shown that a functional length variation in the transcriptional control region of the serotonin transporter gene (5-HTTLPR) influences brain function (Pezawas et al., 2005; Heinz et al., 2005; Canli et al., 2005), personality traits (Munafò et al., 2005; Sen et al., 2004), and susceptibility to psychiatric disorders (Karg et al., 2011).

In the behavioral studies, S allele is often associated with increased levels of anxiety-related traits (Lesch et al., 1996; Munafò et al., 2005; Sen et al., 2004), and risk of depression and mood disorders (Kato, 2007) especially in the context of environmental stress (Karg et al., 2011), but some studies does not confirm these interactions (Risch et al., 2009).

The effects of genes are not expressed directly at the level of behavior but are rather are mediated by effects on brain structure and function. Functional neuroimaging using functional magnetic resonance imaging, EEG, or positron emission tomography, have the potential to explore the brain-relevant genetic polymorphisms by quantifying the activity of specific brain regions in association with particular tasks or states. Based on the above mentioned behavioral findings, functional neuroimaging has been used mainly to reveal association between 5-HTTLPR polymorphism and brain activation in regions associated with affective processing. A number of fMRI studies revealed the association between the S allele and increased amygdala reactivity in both healthy volunteers ((Hariri et al., 2002; Babiloni et al., 2006a, 2006b;

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Dannlowski et al., 2010) and patients with mood disorders (Domschke et al., 2006; Furmark et al., 2004). Importantly, these biological relationships have been revealed and replicated in relatively small samples of subjects, underscoring the power of a direct assay of brain physiology in exploring the functional impact of genetic variation (Hariri and Weinberger, 2003). Other studies extended these reports by showing that 5-HTTLPR genotype modulates functional coupling between the amygdala and medial prefrontal cortex (Pezawas et al., 2005; Heinz et al., 2005), structural differences in frontal cortical regions and anterior cingulate, and that it plays a role in cognitive processes that go beyond reactivity to affective stimuli (Canli et al., 2005).

At present, a growing literature implicates 5-HTTLPR polymorphism in mediating individual differences in cognitive characteristics (Homberg and Lesch, 2011). Carriers of the short allele outperformed L/L carriers in the Wisconsin Card Sorting Test (Borg et al., 2009), in the Go/NoGo-performance (Roiser et al., 2007), continuous performance task (Strobel et al., 2007), working memory (Anderson et al., 2012) and are characterized by higher creativity and intelligence (Volf et al., 2009, 2015c). In decision-making, carriers of the short allele showed reduced financial risk taking (Crişan et al., 2009), and greater attention to differences in the probability of winning (Roiser et al., 2006). At the same time, gender and age has been demonstrated to moderate the association between the 5-HTTLPR polymorphism and various behavioral, emotional, and physiological characteristics (Du et al., 2000; Mizuno et al., 2006; Stoltenberg and Vandever, 2010). In particular, it is known that hormones secreted by the ovaries have a suppressive effect on the expression of the serotonin transporter gene (Bethea et al., 2002) and serotonin 1 A receptors (Wissink et al., 2001). Estradiol and progesterone modify the effects of the serotonin transporter gene polymorphism on serotoninergic responsivity to serotonin reuptake inhibitor citalopram (Michopoulos et al., 2011). These data suggest that the association of 5-HTTLPR polymorphism with physiological characteristics can vary in young and in older postmenopausal women.

There is a substantial body of evidence showing that the success of mental processes, susceptibility to affective disorders, and the effects of antidepressants are associated with a particular profile of the baseline electrical and metabolic activity of the brain (Buckner and Vincenta, 2007). Currently, however, there are a few works to study the association of polymorphism 5-HTTLPR with the characteristics of the background EEG (Bismark et al., 2010; Lee et al., 2011; Volf et al., 2015a). Our previous study reported that effects of 5-HTTLPR polymorphism on EEG spectral power vary as a function of gender (Volf et al., 2015a). Many studies have shown that physiological aging in adults is associated with changes in the power of EEG rhythms at rest (Niedermeyer, 1993; van Sweden et al., 1993; Volf and Gluhih, 2011.). By increasing our sample number in comparison with previous study (Volf et al., 2015a) it became possible to study age and genotype related differences in baseline EEG of women. In the first step we performed the analysis of age differences in association between 5-HTTLPR polymorphism and EEG power. It has been shown that in S′/S′ (LG allele was grouped with S alleles owing to its functional equivalence and this group was labeled as S′) and L/L (LA/LA) genotypes carriers' women of the older age group had lower delta, alpha2 and alpha3 band global power than the young, while S′/L genotype was characterized by higher beta1 rhythm power in elderly compared to young. No significant difference in spatial organization of EEG power between young and older women with different genotypes were found (Volf et al., 2015b). It is known that EEG recordings sample a volume conducted, spatially degraded map of neural activity (Onton et al., 2006), whereas sLORETA (Standardized Low Resolution brain Electromagnetic Tomography) is a validated neuroimaging method for localizing the electric activity in the brain based on multichannel EEG recordings. Besides, the mass-univariate statistical testing that is used in sLORETA is more sensitive to local effects than ANOVA, which is used in channel-level EEG analysis (Friston, 1997). In this regard, the aim of the present investigation was to determine the association of polymorphism 5-HTTLPR serotonin transporter gene and the regional characteristics of generating EEG sources in young and older women on the basis of sLORETA.

2. Material and methods

2.1. Subjects

Right-handed young (YW, $N = 86$, age range: 18–35 years) and older (OW, $N = 45$; age range: 55–80 years) Caucasian women participated in the study. It was the same sample as in our previous investigation (Volf et al., 2015b) with the addition of the two new participants. Graduate and postgraduate students, technicians, administrative and scientific staff of Novosibirsk State Universities and Novosibirsk State Research Institutes of the Russian Academy of Sciences were engaged in the study. All non-students were full time employed high-functioning individuals. For all of the subjects periodic health evaluations were conducted every two years by medical staff unconnected to the study. So, participants had objective information about their health status. The menopausal status and exclusion criteria were based on self-report. Subjects were excluded if they had concussion, suffered from neurological or psychiatric diseases and major medical illnesses (cancer, diabetes, and infarct). All OW but none of the YW were in post-menopausal stage. There were no persons with alcohol or drug dependence. Only one woman in OW group used to smoke. All participants gave informed consent to the study. The study has been approved by the local Institutional Ethics Committee and conformed to the principles of the Declaration of Helsinki.

2.2. EEG recording

During the EEG recording, subjects were sitting in a soundproof and dimly illuminated room. The procedure of EEG registration consisted of 6 one-minute recordings (3 with eyes closed and 3 with eyes open). Only the eyes closed recordings were analyzed in this study because higher heredity of the EEG spectral power in the eyes closed condition has been shown (Anokhin et al., 2006).

The EEG data were recorded using 60 silver-silver chloride electrodes mounted in an elastic cap on the positions of the modified version of the international 10/20 System (American Electroencephalographic Society, 1991). Data were digitized at a rate of 1000 Hz and amplified using “Neuroscan (USA)” amplifiers with a gain of 250 and a band pass of 0 to 70 Hz. All recordings were performed using a frontocentral electrode as the ground, and a nose electrode as the reference. To control eye movements the horizontal and vertical electrooculogram was registered. Electrode impedances were below 5 kΩ. Independent component analysis via the EEGLAB toolbox http://www.sccn.ucsd.edu/eeglab/) was used to reject artifacts from EEG data. The number of artifact-free epochs (mean 86.7, SE = 0.2) did not differ across Age x Genotype groups. The bandwidths for the eight frequency bands were defined using individual alpha peak frequency (IAF) as the anchor point: 1 to (IAF-6); (IAF-6) to (IAF-4); (IAF-4) to (IAF-2); (IAF-2) to (IAF); IAF to (IAF + 2); (IAF + 2) to 20 Hz; 20 to 30 Hz; and 30 to 45 Hz (Doppelmayr et al., 1998). These individually adjusted frequency bands are termed delta, theta, alpha1, alpha2, alpha3, beta1, beta2, and gamma, respectively. Cortical sources of EEG activity were estimated with sLORETA (Pascual-Marqui, 2002). The sLORETA is a linearly distributed solution that is based on standardized values of the current density estimates given by the minimum norm solution. The sLORETA functions on the assumption that the scalp EEG measures are generated by highly synchronized post-synaptic potentials occurring in large clusters of neurons (Pascual-Marqui, 2002). The solution space is restricted to gray matter cortical and hippocampal areas. The sLORETA yields images of standardized current source density of a total of 6430 voxels at 5-mm spatial resolution. Artifact-free epochs of 1.5 s were supplied for cross-spectrum calculation in sLORETA. Subsequently current source densities