Interaction between 5HT1a Receptor Alleles, PSWQ, and Frontal EEG Asymmetry

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Abstract

Anxiety and depression are commonly comorbid phenotypes and are often treated using similar methods. Given serotonin’s dominant role in pharmacological treatment of psychopathology, it is thought to be an important neuro-modulator of mood and arousal. It has also been hypothesized that serotoninergic risk alleles in the 5HT1a receptor gene may be associated with risk for psychopathology when faced with life stressors. The current study examined the relationship between serotonin 5HT1a alleles, depression history, worry (as measured by PSWQ) and their interactive effects on resting frontal electrical brain asymmetry. The sample consisted of 226 (31%) male Caucasian individuals with (n=110) and without (n=116) a history of depression. EEG was assessed from 64 scalp sites on four days (two 8-hour methods each day). Although the main effect of genotype on asymmetry across frontal regions indicated that the risk genotype was associated with greater relative right frontal activity, a significant interaction between PSWQ and 5HT1a genotype emerged. Pairwise comparisons indicated the 5HT1a risk genotype was associated with greater relative right frontal activity more strongly among those with low compared to high worry (significant at channel pairs F7/8, F3/4 and F1/2 with a trend at F3/6). These results indicate the importance of evaluating genetic contributions to psychosocial risks, but also their relationship to comorbid phenotypic worry.

Introduction

q Depression and anxiety are often comorbid phenomenologies, which involve similar neural systems and respond to similar psychosocial and psychopharmacological interventions.
q Genetics play substantial roles in determining both structural and functional capabilities of these neural systems. As such, genetic factors contribute to subtle physiological differences that may serve as a risk endophenotypes for mental illness.
q Frontal EEG asymmetry has been proposed as such an endophenotype for depressive illness (e.g., Allen, Urry, Hitt, & Coan, 2004), but also similar patterns are seen in anxious individuals prone to worry (Effer, Nicolle, & Fiore, 1998).
q According to prevailing models of frontal EEG asymmetry, relative right frontal activity (compared to left) corresponds to withdrawal-oriented motivation/action as well (panic), whereas relative left frontal hemisphere activity in related to approach-oriented motivation/action and anxious apprehension (worry).
q Given the high comorbidity of anxiety & depression, similar treatment approaches are used for each psychopathology and their comorbidity, the most common being serotonin modulation via selective serotonin reuptake inhibitors (SSRI) or serotonin partial agonist (buspirone).
q Research has indicated associations between serotoninergic system alterations and patterns of frontal asymmetry (Bismark, Stewart, Towson, Coan, Erickson, & Allen, under revision; Allen, McKnight, Moreno, & Delgado, 2002; Bruder, G. E., Stewart, J. W., Tenke, C. E., McIntosh, P. J., Leite, P., Bhattacharya, N., et al., 2001).

Research Questions:

q Does the number of 5HT1a risk alleles result in alterations in neural encoding that create a shift towards relatively greater right frontal activity?
q If so, is this pattern of frontal asymmetry moderated by reported symptoms of depression and/or worry?

Methods

Subjects:

q 226 Caucasian non-hispanic participants (157 females) aged 18-33 (M=19.22, SD=.46) were enrolled following offline ocular rejection of vertical EOG amplitude greater then ±75mv, data were segmented to form 2.048 s epochs, windowed with a Hamming taper, and power in alpha frequency band (8-13Hz) was calculated for each channel pair. Significant differences between responders and nonresponders to an electroencephalographic and perceptual asymmetry differences between responders and nonresponders to an electroencephalographic and perceptual asymmetry differences between responders and nonresponders to an electroencephalographic and perceptual asymmetry differences between responders and nonresponders to an electroencephalographic and perceptual asymmetry differences between responders and nonresponders to an electroencephalographic and perceptual asymmetry differences between responders and nonresponders.

Positive Correlation

q Interactions of genotype (risk vs non-risk) and lifetime history of Major Depression (MDD) (positive or negative) predicting asymmetry score at each channel pair.

Results

Figure 1: Main effect of genotype (risk vs non-risk) predicting asymmetry score at each channel pair. Significant at every channel pair F7/8, F5/6, F3/4 & F2/12 with largest effect at channel pair F5/6.

Discussion

q These findings support a relationship between serotonin receptor genetics and frontal EEG asymmetry. Individuals homozygous for 5HT1a genotype (GG) compared with heterozygous (GC) and homozygous (CC) showed relatively greater right frontal activity.
q Both depressed history and measures of worry independently moderate the genotype-asymmetry relationship, suggesting that frontal asymmetry may be sensitive to both enduring genetically-influenced risk patterns, as well as current symptom profiles. This would then suggest that it as an endophenotype of risk may be complementary samples with high worry.
q Similarly, the strength of the genotype-asymmetry relationship is enhanced in those with a history of depression, again suggesting that asymmetry may be sensitive to multiple influences, only some of which are genetic. The finding that asymmetry is related to genetic risk in those with no history of depression, however, supports its utility as a risk endophenotype among those who have not already developed MDD.
q These data also suggest possible risk mechanisms for depression and worry via genetic contributions to alterations in cytoarchitecture that affect not only the structure but efficacy of serotonergic systems, and manifest in asymmetric frontal brain activity.
q In animal models, MDD has been shown to induce rapid increases in excitatory postsynaptic potentials (EPSPs) in pyramidal cells, predominantly in the medial PFC and other frontal enervated regions.
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References