Serotonergic Receptor Genetics: Contributions to EEG Asymmetry

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Abstract

Serotonin is thought to be an important neuro-modulator of mood and arousal. Accumulating evidence indicates that certain serotonin genes (via “risk” alleles) can convey subtle changes in serotonin system architecture that may place an individual at risk for mood and arousal dysregulation, which can manifest as frontally based stress-related symptoms. The current study investigated the relationship between allele variations in the serotonin receptor gene 5HT1a and frontal brain electrical asymmetry. It was hypothesized that different serotonin receptor genotypes (5HT1a) would show a greater relative shift in EEG activity with respect to current clinical state. The sample consisted of 220 Caucasian non- Hispanic college age participants. Genotypes were classified as lifetime history positive (any episode of Major Depression, N=110) or negative (no such episodes, N=115). Results: Subjects classified by number of risk alleles: Homozygous risk (G/G) vs heterozygous risk (G/C) & homozygous non-risk (C/C) regardless of history status, and the smaller number of history positive cases. The results provide support for a genetic contribution to a trait-like EEG asymmetry. Subjects with more 5HT1a risk alleles had greater relative frontal EEG activity at sites F7/8, F5/6, & F1/2, with marginal significance at F3/4, and the largest effect at F5/6. These results support the hypothesis that variation in serotonin receptor genetics (5HT1a) can influence trait level brain activity which may ultimately be indicative of risk for psychopathology.

Introduction

Depression is a heterogeneous illness with individual phenotypes indicating little about illness etiology, but indicating multiple disease pathways and the interactions of genes and environment. Genetics play substantial roles in determining both structural and functional capabilities of neural systems. As such, genetic factors contribute to subtle physiological differences that may serve as a risk endophenotypes for mental illness. Frontal EEG asymmetry has been proposed as such an endophenotype (e.g., Allen, Ury, Hin, & Coan, 2004) as individuals with any depressive history show relatively greater right frontal EEG activity than those without this history.

According to prevailing model of frontal EEG asymmetry, relative right frontal activity (compared to left) corresponds to withdrawal-oriented motivation/action; whereas relative left frontal hemisphere activity in related to approach-oriented motivation/learning. The degree of this difference is indicative of individual differences in stress-responsiveness.

It is unlikely any single neurotransmitter system is responsible for the EEG asymmetry alterations in depression; however, in animal models, 5HT has been shown to induce rapid increases in excitatory post synaptic potentials (EPSPs) in pyramidal cells, predominantly in the medial PFC and other 5HT enriched frontal regions. Previous research indicates lower 5HT1a receptor concentrations in suicide attempts and depressed patients (Arias et al. 2006), combined effects with SERT “S” allele in treatment refractory depressed patients (Agdal 2005), decreased binding potential and agonist response in VIVO (Lepic, 1992).

Research Questions:

1. Does the number of 5HT1a risk alleles result in alterations in neural encoding that create a shift towards relatively greater right frontal activity, regardless of clinical state?

2. Is this effect moderated by depressive history, such that the impact of the 5HT1a risk alleles is potentiated in those with a history of depression?

Methods

Subjects: 220 Caucasian non-hispanic participants (156 females) aged 18-33 (M=22.12, SD=.46) were enrolled following structured clinical interviews. Other than current Major Depressive Disorder (n=105), subjects were free of active Axis I psychopathology. Participants were classified as lifetime history positive (any episode of Major Depression, N=110) or negative (no such episodes, N=115).

Genes: 5HT1A receptor gene: Cytosine to Glycine (C/G) SNP at location -1019 from ATG start in coding region. G is considered risk allele.

Results (cont.)

Statistical Analysis:

α=0.05.

Follow up research is warranted to ascertain the extent of this risk

Supplementary Analysis:

These data further support the potential utility of frontal EEG asymmetry as an endophenotype of risk for psychiatric disorder, and suggest the promise of identifying individuals at risk and also aid in assessing symptoms and treatment response. In addition, this endophenotype could identify individuals for trials of prophylactic interventions.

Results

Electrophysiology:

Tests of between-subjects effects yielded a main effect of genotype (p=.04, p<.01), and within-subjects effects yielded a main effect for channel with all channels differed from one another (F(3,216)=28.43, p<.001). There was no main effect of depressive history status, F(1,216)=1.60, p>.05.

There was also a significant genotype by channel interaction, with significant gene effects at channels F7/8, F5/6 and F1/2 with a trend at F3/4. Pairwise comparisons indicate (G/G) genotype predicts relative right frontal activity. (See Figures 1 & 2).

Supplemental analysis indicated a significant three-way interaction (Genotype x History x Channel), with the G/G History interaction significant at F7/8, with a trend at F5/6. (Figures 3 & 4). This interaction indicates that individuals with the (G/G) genotype show significantly more relative right frontal activity then (C/C) or (G/C) genotype for history negative subjects. This effect is not statistically significant in history positive subjects.

Discussion

These findings support a relationship between serotonin receptor genotype and frontal EEG asymmetry. Individuals homozygous for 5HT1a genotype (G/G) compared with homozygous (C/C) and heterozygous (C/G) showed relatively greater right frontal activity.

Depressive history moderated this effect only at lateral frontal sites. A history of depression, however, was not found to potentiate the effect. In fact, individuals with (G/G) genotype but without a depressive history showed even greater relative right frontal resting activity.

The direction of the difference between risk genotypes was the same regardless of history status, and the smaller number of history positive subjects in part, may be a result of the non-significant relationship to risk status within the history positive sample.

These results argue that if frontal asymmetry may function as an endophenotype that is not dependent on having had a history of depression.

This data suggest possible risk mechanisms for depression 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.

Individuals with risk genotypes may not necessarily experience mood disturbance simply as a function of genotype. However, those same individuals could be at a disadvantage when faced with life stress. Less efficient serotonergic systems would be more likely to break down under greater allostatic load, thus placing the individual at risk for the development of depression.

Follow up research is warranted to ascertain the extent of this risk convevancy, particularly, tracking over time individuals considered at risk for depression based on genotype and resting brain activity.

These data further support the potential utility of frontal EEG asymmetry as an endophenotype of risk for psychiatric disorder, and suggest the promise of identifying individuals at risk and also aid in assessing symptoms and treatment response. In addition, this endophenotype could identify individuals for trials of prophylactic interventions.

References


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