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. It has been hypothesized that variations in certain serotonin genes (via "risk" alleles) can convey subtle changes in serotonin system architecture that may place an individual at risk for psychopathology when faced with life stressors. The current study investigated the relationship between allele variations in the serotonin receptor gene 5HT1a and frontal brain electrical asymmetry. It was hypothesized that individuals homozygous for the risk allele (G/G) will show a relative right shift in EEG activity regardless of current clinical state. The sample consisted of 220 Caucasian non-hispanic college age participants, spanning a range of depressive severity from no symptoms to clinical levels. Resting EEG was recorded from 64 scalp sites on four days (two 8-min periods each day). Alpha asymmetry scores between homologous sites were calculated for each session and then averaged to form a trait metric of asymmetry for each pair. The results provided support for a genetic contribution to a trait-like EEG asymmetry. Subjects with more 5HT1a risk alleles had greater relative right frontal EEG activity at sites F7/F8, F5/F6, & F1/F2; with marginal significance at F3/F4, and the largest effect at F5/F6. 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, Urry, Hitt, & 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/action and may be 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 postsynaptic potentials (EPSPs) in pyramidal cells, predominantly in the medial PFC and other 5HT enriched frontal regions.
- Previous research indicates lower 5HT1A receptor concentration in animal models of depression (Iritnai et al. 2006), combined effects with SERT "S" allele in treatment refractory depressed patients (Arias 2005), and decreased binding potential and agonist response in vivo (Lopez, 1998).

Research Questions:

- 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?
- 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=19.22, 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=105) 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.**
- Subjects classified by number of risk alleles: Homozygous risk (G/G) vs heterozygous risk (G/C) & homozygous non-risk (C/C)

Electrophysiological Data Collection & Processing:

- Resting EEG data were collected on four separate days within a 14-day window, two 8-minute periods each day.
- EEG was recorded continuously using 64-channel EEG cap with 1K Hz sampling rate (bandpass 0-200 Hz) using online reference just posterior to Cz, re-referenced offline to averaged-mastoids.
- Following offline ocular rejection of vertical EOG amplitude greater then ±75mv, data were segmented to 2.048 s epochs, windowed with a Hamming taper, and power in alpha frequency band (8-13Hz) was extracted via Fast Fourier transformed (FFT).

Frontal Asymmetry:

- Alpha asymmetry scores, ln-transformed subtractions (ln[Right]-ln[Left]) between homologous sites for each session, were averaged across days and sessions to give a trait measure of alpha activity for each pair for each subject. Only the following frontal channel pairs were statistically examined: F1/2, F3/4, F5/6 & F7/8

Statistical Analysis:

- A Repeated measures General linear model (GLM) with channel pair and risk status was used to assess whether genotype could predict frontal asymmetry score, regardless of depressive history

Supplementary Analysis:

- An additional GLM tested whether any effects in the primary analysis were moderated by depressive history (positive or negative), in a model with channel pair, risk status, and depression history status as factors. The Greenhouse-Geisser correction for violations of the sphericity assumption were used. In all cases, original degrees of freedom are presented, along with the epsilon-corrected p-values

Results

Electrophysiology:

- Tests of between-subjects effects yielded a main effect of genotype F(1,216)=6.954, 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 F(1,216)=.610, 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 Gene x 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 (C/G) genotype for history negative subjects. This effect is not statistically significant in history positive subjects.

Figure 1. Correlations reveal the magnitude of the relationship between frontal EEG asymmetry and genetic risk status. Negative values indicate that the risk genotype is associated with greater relative right frontal activity. (*=p<.05, †=p<.10)

Results (cont.)

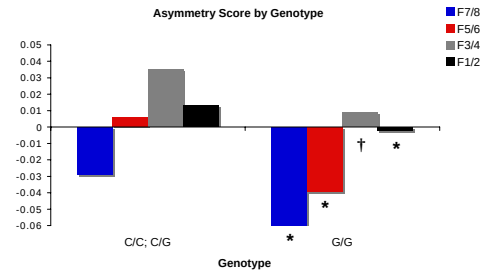

Figure 2: Asymmetry scores by site by genotype collapsed across depressive history. Individuals with genotype (G/G) show significantly more relative right EEG activity than individuals with genotype (C/C) or C/G). This is significant at pairs F7/8, F5/6 & F1/2 with a trend at F3/4. Symbols indicate differences between genotypes at a given channel pair (*=p<.05, †=p<.10).

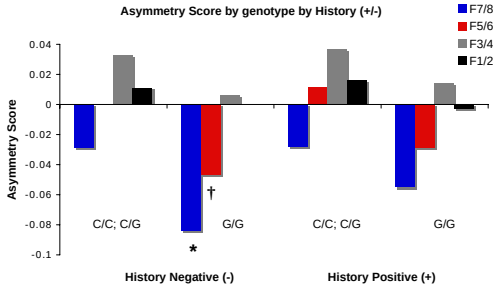

Figure 3: Asymmetry scores by site by genotype by depressive history (+/-). Individuals with 5HT1a receptor genotype (G/G) show more relative right EEG activity when compared to genotypes (C/C) & (C/G). The presence of a depressive history moderates the relationship between genotype and frontal asymmetry at F7/8, with a trend at F5/6. Symbols indicate differences between genotypes at a given channel pair for history negative subjects (*=p<.05, †=p<.10)

Figure 4. Correlations reveal the magnitude of the relationship between frontal EEG asymmetry and genetic risk status for individuals *without* a history of depression. Negative values indicate that the risk genotype is associated with greater relative right frontal activity. (* = p<.05)

Figure 5. Correlations reveal the magnitude of the relationship between frontal EEG asymmetry and genetic risk status *with* a history of depression. Negative values indicate that the risk genotype is associated with greater relative right frontal activity. (* = p<.05)

Discussion

- These findings support a relationship between serotonin receptor genetics 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 may have been, in part, responsible for the nonsignificant relationship to risk status within the history positive sample.
- These results argue that that frontal asymmetry may function as an endophentype 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 conveyance, 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.

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