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

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## Abstract

Anxiety and depression are commonly comorbid psychopathologies 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 serotonergic 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, depressive 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-min periods 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 worry compared to high worry (significant at channel pairs F7/8, F3/4 and F1/2 with a trend at F5/6). These results indicate the importance of evaluating genetic contributions to psychophysiological risk metrics, but also their relationship to comorbid phenotypic worry.

## Introduction

- Depression and anxiety are often comorbid phenomenologies, involve similar neural systems and respond to similar psychosocial and psychopharmacological interventions.
- 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.
- 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 (Heller, Nitschke, Etienne & Miller, 1998).
- According to prevailing model of frontal EEG asymmetry, relative right frontal activity (compared to left) corresponds to withdrawal-oriented motivation/action as well as anxious arousal (panic); whereas relative left frontal hemisphere activity in related to approach-oriented motivation/action and anxious apprehension (worry).
- 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 agonism (buspirone).
- Research has indicated associations between serotonergic system alterations and patterns of frontal asymmetry (Bismark, Moreno, Stewart, Towers, Coan, Oas, Erickson & Allen, under revision; Allen, McKnight, Moreno, Demaree & Delgado (2009); Bruder, G. E., Stewart, J. W., Tenke, C. E., McGrath, P. J., Leite, P., Bhattacharya, N., et al. (2001)).
- While it is unlikely any single neurotransmitter system is responsible for the EEG asymmetry alterations seen in depression or anxiety; 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.

***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?
- If so, is this pattern of frontal asymmetry moderated by reported symptoms of depression and/or worry?

## Methods

***Subjects:***

- 226 Caucasian non-hispanic participants (157 females) aged 18-33 (M=19.22, SD=.46) were enrolled following structured clinical interviews. Other than current Major Depressive Disorder, 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=116) based on SCID clinical interviews.

***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 non-risk (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 transform (FFT).

***Frontal Asymmetry:***

- Alpha asymmetry scores, the difference in ln-transformed alpha power (ln[Right]-ln[Left]) between homologous sites for each session. Only the following frontal channel pairs were statistically examined: F1/2, F3/4, F5/6 & F7/8

***Statistical Analysis:***

- Correlations: Life Time MDD & PSWQ-score
- Mixed Linear Models at each of 4 channel pairs:

DV: Asymmetry Score at each channel pair

IVs: Day, Session, MDD Hx (+/-) & Genetic Risk (+/-)

Covariate: Z-Scored Penn State Worry Questionnaire (PSWQ)

***Supplementary Analysis:***

- Additional Mixed Models were used to test effects of high (+1 SD) and low (-1 SD) reported symptoms of anxiety (PSWQ scores) on gene risk and frontal asymmetry. Pairwise comparisons utilized to investigate direction of interaction(s).

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## Results

📖 Correlation: Lifetime MDD X PSWQ: r = 0.39, p<0.001

***Electrophysiology:***

Main Effects:

- Genotype F(1, 1701) =14.8, p<0.001

Interactions:

- Genotype X PSWQ F(1, 1701) =19.9, p<0.001*
- Genotype X Lifetime MDD F(1, 1701) =5.0, p<0.03*
- Genotype X PSWQ X Lifetime MDD F(2, 1701) =0.96, p>0.38

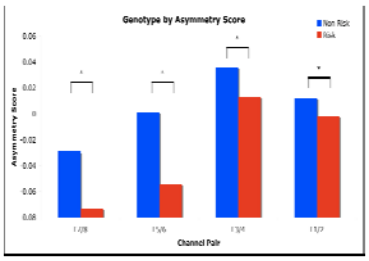


*Figure 1*: Main effect of genotype (risk vs non-risk) predicting asymmetry score at each channel pair. Significant at every channel pair F7/8, F5/6 F3/4 & F1/2 with largest effect at channel pair F5/6.

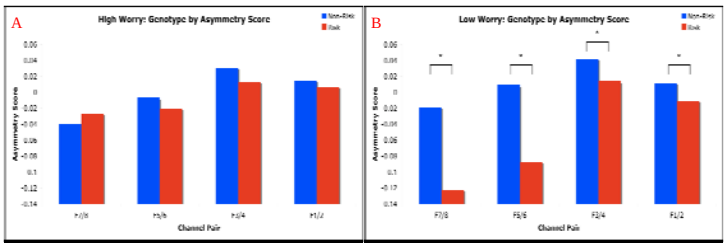


*Figure 2a & b*: Interactions of genotype (risk vs non-risk) and Z-scored PSWQ scores (1 SD+ & 1SD-) predicting frontal asymmetry.
*Left (A)*: PSWQ (1SD+) by genotype interaction, non-significant at any channel pair.
*Right (B)*: PSWQ (1SD-) by genotype interaction, significant at all channel pairs F7/8, F5/6, F3/4 & F1/2, largest effects at lateral sites.

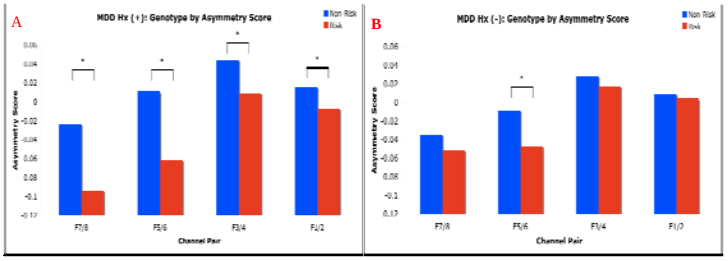


*Figure 3a & b*: Interactions of genotype (risk vs non-risk) and lifetime history of Major Depression (MDD) (positive or negative) predicting frontal asymmetry scores.
*Left (A)*: MDD (-) by genotype interaction, significant only at channel pair F5/6.
*Right (B)*: MDD(+) by genotype interaction, significant at all channel pairs F7/8, F5/6, F3/4 & F1/2.

## 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.
- Both depressive history and measures of worry independently moderated 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 its use as an endophenotype of risk may be compromised in samples with high worry.
- 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 still 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.
- 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.
- 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 serotonin enriched frontal regions (Marek & Aghajanian, 1998).
- Midbrain raphe neurons, rich in 5HT1a receptors, innervate pyramidal neurons in the PFC, which themselves project downward to innervate areas such as anterior cingulate and basal ganglia. Recursive dysregulation of these cortico-limbic circuits are thought to explain differences in resting brain activity seen in depression and worry via their down stream effects on related brain regions.
- These data imply genotypic mechanisms influence brain structure and function that are being tapped by frontal EEG asymmetry. Whether these mechanisms manifest directly as psychopathology are more likely dependent on other moderating factors such as life stress.

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