Associations Between Serotonin Transporter (SERT) Risk Alleles & Parietal EEG Asymmetry

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Abstract

- Serotonin is thought to be a powerful neuro-modulator of mood and arousal due to its role as an important target in the pharmacological treatment of psychopathology such as depression & anxiety. Over the past decade, the serotonin transporter (SERT) has been the subject many investigations as a genetic marker for risk for developing psychopathology, with mixed findings. Research also suggests that parietal EEG asymmetry may be used as a marker for risk for developing psychopathology (Stewart et al, in press), with individuals who demonstrate greater relative left parietal activity hypothesized to be at greater risk. The current study investigated the relationship between the serotonin transporter insertion/deletion ("long" and "short") to patterns of regional electrical brain activity. The sample consisted of 306 volunteers (31% male) aged (18-34). EEG was assessed from 64 scalp sites on four days (two 8-min periods each day), and transformed to current-source density prior to extraction of alpha band activity via FFT. There was a main effect of SERT genotype such that individuals who carried at least one copy of the short (risk) allele showed greater relative left parietal activity (less left parietal alpha) at channel pairs P7/8, P5/6, P3/4 & P1/2. These results indicate the importance of genetic contributions to psychophysiology and possible 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.
- Parietal EEG asymmetry has been proposed as such an endophenotype (Stewart et al. 2010) as relatively lower right resting parietal EEG activity (inferred by relatively greater right alpha band activity); distinguishes both symptomatic and remitted depressed individuals from never-depressed individuals (Blackhart, Minnix, & Kline, 2006; Bruder et al., 1997)
- The Serotonin transporter gene (SLC6A4) is another possible endophenotype, whose variants have been the subject of much research linking affective disorders and impaired emotional stimulus processing to its "short" allele variant (see Caspi et al. 2010 for review).
- However, little work has been done on SERT's endophenotypic possibilities by linking its variants with non task-related (or resting state) neural function in relation to risk for psychopathology.
- The current study aims to unify these two literatures by investigating the relationship between parietal EEG asymmetry, SERT variant alleles and psychopathology.

Research Questions:

- Is there a relationship between SERT variant alleles and parietal asymmetry, such that variants associated with depressive risk are associated with relatively less right parietal activity, the pattern associated with risk for depression?
- Is the relationship between SERT variant alleles and parietal asymmetry moderated by MDD status mode or the occurrence of stressful life events?

Methods

Participants:

- 306 volunteers (31% male) aged 18-34 (M=19.2; SD=2.0). 163 participants had a history of Major Depression (MDD+), the other 143 had no history of depressive illness (MDD-).

Genes/Alleles:

- Serotonin Transporter Gene (SERT: SLC6A4): 44bp insertion/deletion results in two distinct alleles, a "long" version, including the 44bp insertion and the "short" version, excluding it. **The short allele is considered the risk allele**.

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 using current source density (CSD) algorithm (Keysar & Tenke, 2006).
- 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).

Parietal Asymmetry:

- Alpha asymmetry scores, ln-transformed subtractions (ln[Right]-ln[Left]) between homologous sites were calculated, providing an asymmetry score for each session and day. The following parietal channel pairs were statistically examined: P1/2, P3/4, P5/6 & P7/8. **Greater values signify relatively greater right alpha power, relatively less right activity.**

Statistical Analysis:

- Mixed Linear Models:
  - DV: Asymmetry score at each channel pair
  - IVs: Day, Session, MDD Hx(+/-) & SERT risk (+/-)
  - Covariate: Z-scored total number of recent life events

Results

Electrophysiology:

- There was a main effect of Genotype significant at all channel pairs. Pairwise comparisons indicated risk genotype predicted relatively greater left parietal activity (Figure 1).
- There was also a significant Genotype by life events interaction significant at all channel pairs, pairwise comparisons again indicating that those individuals with a risk genotype and a high number of stressful life events showed relatively greater left parietal activity (Figure 2).
- Lastly, there was a three-way interaction (Genotype X MDD Hx X Life events) that was significant at channel pairs P3/4 & P1/2 with a near significant trend at P5/6. A breakdown of the interaction by MDD status indicated that individuals with any history of MDD, a risk genotype and who has experienced a high number of stressful life events consistently predicted relatively greater left parietal activity (Figures 3).

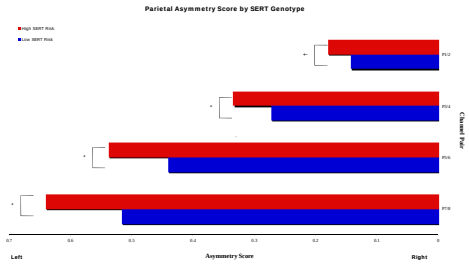


Figure 1: Shows the main effect of SERT genotype on parietal asymmetry. Individuals who carry at least one risk allele demonstrate greater relative left parietal activity then (*ll*) individuals.

Results (cont.)

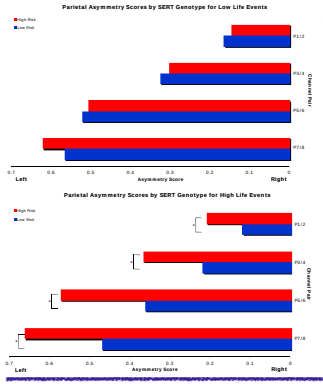


Figure 2: Genotype by stressful life events interaction.

Top panel shows that among individuals who experienced fewer stressful live events over the 6 months prior to study participation, SERT genotype had no effect on parietal asymmetry.

Lower panel shows that among individuals who experienced more stressful live events over the 6 months prior to study participation, SERT risk genotype was associated with relatively less right parietal activity.

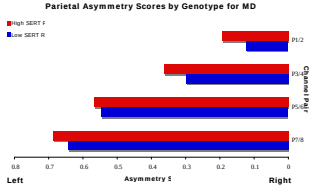
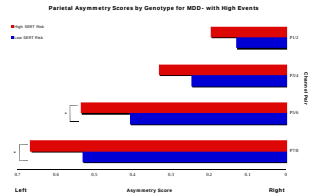
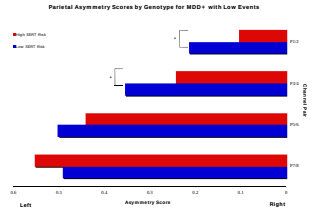


Figure 3: Genotype by MDD History by stressful life events interaction.

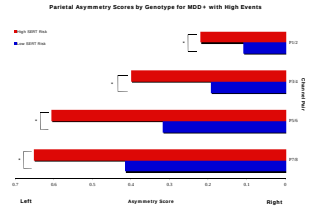
3A: There is no significant effect of genotype among MDD Hx- individuals with few life stressors.



3B: An effect of genotype emerges for those MDD Hx- individuals who experience higher levels of stressful life events, significant at channel pairs P7/8 & P/56



3C: An effect of genotype emerges for those MDD Hx+ individuals who experience low levels of stressful life events, but opposite to the direction predicted, in that individuals without at least one risk allele display relative greater left parietal activity, significant at channel pairs P3/4 & P1/2.



3D: An effect of genotype MDD Hx+ individuals who experience higher levels of stressful life events emerges at all regions. Individuals with at least one risk allele, who have a history of depression & experience more stressful life events, display greater left parietal activity that those who experience lower levels of stressful events.

Discussion

- These findings support a relationship between serotonin transporter gene variants and parietal EEG asymmetry. Individuals who carry at least one copy of the short allele show relatively greater left parietal activity (Figure 1).
- There were significant genotype by stressful live events interactions at each site with risk allele carriers who had experienced a greater number of life events showing relatively greater left parietal activity.
- The relationship between SERT genotype and stressful life events was further moderated by MDD Hx(+/-) such that individuals with a risk genotype, a history of MDD (current of past), and a greater number of stressful life events, consistently display greater left parietal activity compared to their never depressed counterparts.
- Regardless of MDD Hx, 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.
- 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 partially support the potential utility of parietal EEG asymmetry and SERT genetic variants as an endophenotypes of risk for psychiatric disorder, and suggest the promise of identifying individuals at risk who carry either (or both) of these endophenotypes and how life stress may tax a vulnerable diathesis placing an individual at risk for psychopathology or possible relapse.

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