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Polymorphisms of the HTR1a allele are linked to frontal brain electrical asymmetry

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ABSTRACT

Polymorphic variations in genes related to serotonin synthesis, transport, recognition, or degradation may convey subtle changes in serotonin system architecture that may place an individual at risk for psychopathology when faced with life stressors. The relationship between three key serotonin alleles and frontal brain electrical asymmetry, a putative endophenotype of depression, was examined. Risk alleles were hypothesized to predict relatively greater right frontal brain activity regardless of current clinical state. A sample of 313 college-age individuals, spanning a range of depressive severity from no symptomotology to clinically meaningful levels, participated. Resting encephalographic (EEG) activity was recorded from 64 scalp sites on four occasions separated by at least 24 h (two 8-min recording sessions occurring at each occasion). Alpha power asymmetry scores between homologous sites were calculated for each session and then averaged to form a trait metric of asymmetry for each pair. PCR based genotyping was conducted for the HTR1a, HTR2a, and HTTLPR genes. Variations in the HTR1a gene were related to trait EEG asymmetry, regardless of any history of depression. Compared to subjects with at least one non-risk allele, subjects with homozygous HTR1A risk alleles had significantly greater relative right frontal activity at sites F7/F8, F5/F6, and F1/F2. In conclusion, variation in HTR1a can influence trait level brain activity, which may ultimately be indicative of risk for psychopathology.

1. Introduction

Depression has a notoriously heterogeneous presentation, implying diverse disease contributions. Endophenotypes (measurable biological markers of disease conveyance (Gottesman and Gould, 2003; Iacono, 1998)) can aid in elucidating specific risk pathways by parsing the heterogeneity of symptom-based phenotypes into homogeneous clusters that share underlying neurophysiological mechanisms. The current study thus investigated the relationship between a putative endophenotype for depressive risk, frontal electroencephalographic (EEG) asymmetry, and three serotonergic candidate genes that have shown a previous association with depression.

Serotonergic dysregulation is implicated in the onset, course and recovery of depression (Arias et al., 2005; Lesch, 2001), with studies showing an association between genetic polymorphisms in serotonin genes and individuals with depression or at risk for depression (e.g. Brown and Hariri, 2006; Caspi et al., 2003; Ogilvie et al., 1996), but not without exception (Frisch et al., 1999; Kato, 2007). Specific genes of interest in the present study were: (1) the serotonin (5-HT) transporter linked promoter region (HTTLPR) gene polymorphism SLC6A4, located on chromosome 17, with the short polymorphism resulting in a decrease of serotonin transporter efficacy (in binding, reuptake, and mRNA concentrations), and was associated with increased depression in the presence of life stress in early studies (e.g., Caspi et al., 2003 but see Risch et al., 2009); (2) the C(−1019)G polymorphism of the 5HT Receptor-1A (HTR1A) gene, with the G allele showing a two-fold increase in depressed individuals, and the extensive distribution of these receptors in key brain areas associated with depression including prefrontal cortex pyramidal and inter-neurons, hippocampus, amygdala, hypothalamus and septum (Le Francois et al., 2008); and (3) the 5HT Receptor-2a (HTR2a), in which an increased frequency of the C allele polymorphism in exon 1 has been found in individuals with unipolar depression (Zhang et al., 1997). In addition, HTR2a receptors often function within limbic-cortical loops to moderate prefrontal cortex pyramidal neurons. Blockade

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of these HTR2a receptors (e.g. mirtazapine, trazodone, nefazodone, and perhaps atypical neuroleptics) in conjunction with the activation of 5-HTR1a (Santarelli et al., 2003) have been proposed as mechanisms of action for 5-HT reuptake inhibitor antidepressants.

1.1. Frontal functional brain asymmetry and risk for psychopathology

There is a large body of research suggesting the utility of frontal EEG asymmetry as an endophenotype for various psychopathologies. The asymmetry involves relatively greater left-frontal vs right-frontal alpha-band (8–13 Hz) power, implying decreased left-frontal activity, since alpha is seen during periods of cortical quiescence (Allen et al., 2004a, b). Individuals with a history of depression, independent of current clinical status, may be distinguished from never-depressed persons by frontal EEG asymmetry (Stewart et al., under review; Allen et al., 1993; Gotlib et al., 1998; Henriques and Davidson, 1990, 1991; Reid et al., 1998). This asymmetry also characterizes persons potentially at-risk for depression, including infants (Dawson et al., 1997; Jones et al., 1997) and adolescents (Tomarken et al., 2004) of depressed mothers, consistent with the notion that resting frontal EEG asymmetry may tap a diathesis for depression or other emotion-related psychopathology, particularly those associated with high levels of negative affect (for review see Coan and Allen, 2004). Research has established that high negative affect predisposes individuals to both mood and anxiety disorders, and accounts for the majority of comorbidity between them (Clark and Watson, 1991; Watson et al., 2008, 1995). Therefore, prefrontal brain asymmetry appears to be an important risk factor not only for MDD, but also for internalizing disorders more generally, all of which are associated with a predisposition toward high levels of negative affect. In addition to depression, frontal EEG asymmetry has been found to characterize those with: anxious arousal/somatic anxiety (Mathersul et al., 2008; Nitschke et al., 1999; Stewart et al., 2008); panic disorder (Wiedemann et al., 1999); comorbid anxiety and depression (Bruder et al., 1997); social phobia (Davidson et al., 2000); premenstrual related dysphoria (Accortt and Allen, 2006; Accortt et al., under review), seasonal affective disorder (Allen et al., 1993), and a variety of childhood or adolescent internalizing psychopathology (Buss et al., 2003; Fox et al., 1995; Fox et al., 2001; Schmidt and Fox, 1994).

Research has also suggested that prefrontal brain asymmetry is at least partly heritable. In a sample of 732 twins and their siblings, the heritability of prefrontal brain asymmetry was as high as 32% for men and 37% for women (Smit et al., 2007) and approximately 30% in two smaller samples (Anokhin et al., 2006; Coan et al., 2009). A more recent twin sample ($n = 951$) looking at 9–10 year old twins, estimates the heritability of frontal asymmetry at 11–28% (Gao et al., 2009). While the reported heritability of frontal asymmetry in these studies is not large, it is in the range of that observed for depression. The heritability of depression has been estimated to be higher in women than men, and in the range of 22–24% for men (Bierut et al., 1999; McGue and Christiansan, 2003) and 37–39% for women (Kendler and Prescott, 1999; McGue and Christiansan, 2003).

1.2. Serotonin and frontal EEG asymmetry

Bruder et al. (2001) reported global hemispheric differences in alpha band EEG in SSRI responders with a shift from relatively greater left alpha power (relatively greater right hemisphere activity) pre-treatment to no hemispheric differences post-treatment. Examining frontal asymmetry specifically, Allen et al. (2009) examined rapid plasma tryptophan depletion (TD), a procedure that transiently lowers brain serotonin, finding that the magnitude of TD-induced change in frontal EEG asymmetry significantly predicted the development of depression during the ensuing six to twelve months.

1.3. The present study

The present study thus examined the relationship of frontal EEG asymmetry to serotonin allele variations in a large sample of medication-free participants with the hypothesis that genotype risk status would be associated with greater relative right frontal activity. The primary aim of this study was to investigate how functional polymorphisms within specific genes in the serotonin system influence the putative marker of risk for depression, frontal EEG asymmetry.

2. Methods and materials

2.1. Participants

Participants completed the Structured Clinical Interview for DSM disorders (SCID (First et al., 1997)) and were excluded for any DSM-IV Axis I disorder other than Major Depressive Disorder (MDD) or Dysthymia. All participants were strongly right handed (Score > 35 of 39 on a handedness inventory (Chapman and Chapman, 1987)). Exclusionary criteria included history of head injury, loss of consciousness exceeding 10 min, concussion, epilepsy, electroconvulsive therapy and use of current psychotropic medications. Individuals with active or acute suicidal potential necessitating immediate treatment were also excluded. Interview screening and DNA sampling (via salivary collection or buccal cheek swabs) took place on a separate day prior to any EEG evaluations. A total of 323 participants from among 520 invited for screenings were found eligible for participation; ten participants discontinued before beginning any EEG recording. These participants did not significantly differ from the remaining participants in age, gender or ethnicity. The final sample of 313 participants (32% male) aged 18–33 ($m = 19.2$, $sd = 2.0$) included: 74 experiencing current depressive symptomotology at the time of evaluation (52 Major MDD, 14 Dysthymia, 8 Double-Depression), 17 of whom were experiencing their first episode; 72 participants currently not depressed but with a history of depressive illness and 167 participants with no history of depressive illness. These participants are also reported in Stewart et al. (under review).

Gene frequencies as a function of Depression History status are presented in Table 1 for the genes examined in this study. The initial analyses were carried out using all participants with complete gene and EEG data. To assess whether varying rates of gene frequency between ethnicities (Cardon and Bell, 2001; Glatt et al., 2004) might indicate a need to assess an ethnically and racially homogeneous subsample, chi-square analyses were used to evaluate any ethnic stratification of allele frequency per gene. Given the racial/ethnic composition of the sample (72% Caucasian non-Hispanic, 10% Hispanic, 5% Black, 8% Asian, 3% American Indian, 1%

Table 1
Genotype by depressive history for the full sample.

	HTR1a			
	CC	CG	GG	
Hx(−)	48	82	34	$\chi^2 = 0.65$, *ns*
Hx(+)	46	63	32	
Total	94	145	66	
	HTR2a			
	GG	GC	CC	
Hx(−)	31	80	27	$\chi^2 = 0.41$, *ns*
Hx(+)	24	69	33	
Total	55	149	60	
	HTTLPR			
	LL	LS	SS	
Hx(−)	55	84	27	$\chi^2 = 0.67$, *ns*
Hx(+)	47	77	18	
Total	102	161	45	

Note: There were no significant differences in allele distributions as a function of depressive history. Numbers of subjects vary somewhat across alleles (HTR1a = 305, HTR2a = 264, HTTLPR = 308) due to problems in sample collection and/or genetic analysis. For each gene, when dichotomizing for risk vs non-risk, the leftmost and center columns were combined to represent non-risk while the rightmost column was the genotype most associated with risk. For example: HTR1a Non-risk genotype: CC/CG vs risk Genotype: GG.