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Review

Association between a serotonin transporter promoter polymorphism (5HTTLPR) and personality disorder traits in a community sample

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ABSTRACT

Background: The serotonin transporter (SERT) polymorphism (5HTTLPR) has been reported to be associated with several psychiatric conditions. Specific personality disorders could be intermediate factors in the known relationship between 5HTTLPR and psychiatric disorders. This is the first study to test the association between this polymorphism and dimensions of all DSM-IV personality disorders in a community sample.

Methods: 374 white participants were assessed by clinical psychologists using the International Personality Disorder Examination (IPDE). Associations between dimensions of each DSM-IV personality disorder and the long (l) and short (s) alleles of the 5HTTLPR were evaluated using non-parametric tests and regression models.

Results: The *s* allele of the 5HTTLPR polymorphism was significantly associated with higher avoidant personality trait scores in the whole sample. Males with the *s* allele had a significantly lower likelihood of higher obsessive–compulsive personality disorder (OCPD) trait scores, whereas females with the *s* allele were likely to have higher OCPD personality trait scores.

Conclusion: This paper provides preliminary data on the relationship between personality disorders and the 5HTTLPR polymorphism. The relationship of the *s* allele and avoidant PD is consistent with findings of a nonspecific relationship of this polymorphism to anxiety and depressive disorders. Concerning the unusual sexual dimorphic result with OCPD, several hypotheses are presented. These findings need further replication, including a more detailed study of additional variants in SERT.

1. Introduction

Personality disorders are maladaptive and inflexible enduring patterns of perceiving, relating to, and thinking about the environment and oneself, which are exhibited in a wide range of social and personal contexts. These disorders are egosyntonic, cause functional impairment and distress and are relatively stable over time (APA, 1994). To diagnose personality disorders pathological personality traits are assessed. However, these traits typically form a continuous distribution in populations, with no obvious point of rarefaction that would indicate the disorder definition (Livesley et al., 1998; Nestadt et al., 1992). Personality disorders are reported to have a substantial genetic basis (Kendler et al., 2008; Reichborn-Kjennerud, 2010). Results from family studies indicate familial aggregation of personality disorder traits (Asarnow et al., 2001; Hicks et al., 2004; McGirr et al., 2009; Reich, 1989). In addition, from twin studies the estimated heritabilities of individual personality disorders range from 21 to 79% (Coolidge et al., 2001; Kendler et al., 2006; Reichborn-Kjennerud et al., 2007; Torgersen et al., 2000).

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The most comprehensively studied genetic variant in psychiatry is a polymorphism in the promoter region of the serotonin transporter gene (SLC6A4), designated as 5HTTLPR (Caspi et al., 2010; Murphy et al., 2004). The SLC6A4 gene is located on chromosome 17q11.1–17q12, and the encoded protein is an important target of selective serotonin reuptake inhibitors (SSRIs) (Ramamoorthy et al., 1993). Typically, there are two length polymorphisms of 5HTTLPR: a "short" (*s*) allele, with 14 repeats; and a "long" (*l*) allele, with 16 repeats. The *s* allele exhibits lower gene expression, resulting in reduced serotonin transporter (5HTT) expression and serotonin uptake in cells expressing that protein, including neurons, glia, blood platelets, and lymphoblasts (Heils et al., 1996; Greenberg et al., 1999).

The 5HTTLPR polymorphism has been found to be associated with several psychiatric disorders, including affective disorders (Collier et al., 1996), obsessive–compulsive disorder (Bloch et al., 2008), eating disorders (Calati et al., 2010), substance use disorders (Weizman and Weizman, 2000), and attention-deficit disorder (Gizer et al., 2009). Moreover, a systematic review ($n = 2539$) suggested a positive association between the *s* variant and suicidal behavior ($p = 0.009$) (Anguelova et al., 2003). In 1996, Lesch et al. first reported an association between the s allele and anxiety-, depression- and aggression-related general personality traits, using the NEO Personality Inventory (Lesch et al., 1996). Results from a large meta-analysis ($n = 5629$) reported suggestive evidence of an association between the *s* allele and anxiety-related personality trait scores ($p = 0.087$) as measured by several personality inventories; an especially strong association was found between the polymorphism and NEO neuroticism ($p < 0.0001$) (Sen et al., 2004).

However, the relationship between pathologic personality traits, as defined by DSM-III or DSM-IV, and the 5HTTLPR has not been well-studied. Most papers have restricted their focus to a few personality disorders. The *s* allele has been reported to be associated with antisocial personality disorder traits (Garcia et al., 2010; Lyons-Ruth et al., 2007; Reese et al., 2010) and borderline personality disorder traits (Garcia et al., 2010), although findings have been inconsistent (Ishiguro et al., 1999; Liao et al., 2004; Pascual et al., 2008; Ni et al., 2006). Two studies reported association between the *l* allele and higher schizotypal personality traits (Golimbet et al., 2009, 2003). The only study of the relationship between obsessive–compulsive personality and the 5HTTLPR polymorphism failed to find an association (Perez et al., 2006). To the best of our knowledge, no study has investigated the association of the variants of the serotonin transporter gene with all personality disorders.

The aim of the current study was to explore the association of the 5HTTLPR polymorphism and all personality disorders as described in DSM-IV in a community sample from the Hopkins Epidemiology of Personality Disorders Study (HEPS) (Samuels et al., 2002). Since 5HTTLPR allele frequencies have been reported to differ by race (Gelernter et al., 1997, 1998), we restricted the current analyses to white participants. In addition, as there is evidence that sex modulates the influence of the 5HTTLPR on affective functioning (Stoltenberg and Vandever, 2010; Brummett et al., 2008b), we conducted sex-specific analyses.

2. Methods

2.1. Study sample

Subjects participating in the Hopkins Epidemiology of Personality Disorder Study (HEPS) were sampled from the Baltimore Epidemiologic Catchment Area (ECA), which has been described previously (Eaton et al., 1997, 1998). In brief, 3481 subjects were interviewed in 1981, comprising the Eastern Baltimore Mental Health Survey of the ECA. Between 1993 and 1996, 1920 subjects (73% of the surviving sample) were re-interviewed, as part of the Baltimore ECA Follow-up survey. From these individuals, all those who were examined by psychiatrists in 1981, as well as all subjects who were identified by the Diagnostic Interview Survey (DIS) as having a lifetime diagnosis of mania, depression, panic disorder, obsessive–compulsive disorder, alcohol use disorder, or drug use disorder at follow up. In addition, a 25% (222/884) random sample was selected from the remaining subjects. A total of 742 subjects completed the personality examination between 1997 and 1999 in the HEPS study (Samuels et al., 2002) reported in this paper. The study was approved by the Institutional Review Board of Johns Hopkins Medical Institutions. Prior to the interview, participants provided informed consent for study procedures, including the interview and collection of a DNA sample.

2.2. Clinical assessment

DSM-IV personality disorder traits were assessed by four masters-level clinical psychologists using the International Personality Disorder Examination (IPDE) between 1997 and 1999. The IPDE is a validated semi-structured interview with demonstrated inter-rater reliability and temporal stability used to diagnose personality disorders (Loranger et al., 1994). All DSM-IV personality disorders were evaluated. Each trait was rated absent (0), accentuated or exaggerated (1), criterion level (2) or missing/unknown (9). To obtain additional information, the subjects' relative or friend was interviewed. In forty jointly rated interviews, the intraclass correlation coefficients for number of DSM-IV personality criteria rated 1 or 2 were: schizoid (0.81), schizotypal (0.58), paranoid (0.63), antisocial (0.80), borderline (0.76), histrionic (0.62), narcissistic (0.62), avoidant (0.89), dependent (0.76), and obsessive–compulsive (0.70). Psychiatric evaluations were conducted by five psychiatrists who examined participants using an adapted version of the Schedule for Clinical Assessment in Neuropsychiatry (SCAN, version 1.5) (Wing et al., 1990) for current and lifetime disorders according to DSM-IV criteria (APA, 1994).

2.3. Genotyping

HEPS participants were sampled by venous blood or cheek swab if they did not want to provide a venous sample. Subjects who agreed to provide DNA were sampled by finger-stick onto a specially formulated "Isocode" Card. DNA was isolated from peripheral blood leukocytes using Puregene Blood Kit chemistry on an Autopure LS automated DNA purification instrument (Qiagen, Valencia, Calif). Buccal swabs were isolated manually using a Puregene DNA isolation kit (Qiagen) following manufacturer's protocol. Blood collected on Isocode Cards was isolated according to the manufacturer's instructions by heating hole punches (made by the American Red Cross) in distilled water at 95 °C for 30 min. DNA concentrations were determined by spectrophotometry using a DU 530 Life Science UV/Vis Spectrophotometer (Beckman Coulter, Brea, California). The 5HTTLPR genotype was determined by polymerase chain reaction amplification (polymerase chain reaction primers and conditions are available upon request).

A total of 628 (85%) of the 742 participants provided a DNA sample and were genotyped for 5HTTLPR. The 114 un-genotyped subjects had similar distributions of race, age, sex and marital status and had more years of education compared to genotyped subjects; however, the level of education was not related to the 5HTTLPR allele distribution. The distribution of 5HTTLPR genotypes