Arch Womens Ment Health (2010) 13:417–423
DOI 10.1007/s00737-010-0164-4

ORIGINAL ARTICLE

Neuroticism-related personality traits are related to symptom severity in patients with premenstrual dysphoric disorder and to the serotonin transporter gene-linked polymorphism 5-HTTPLPR

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Received: 17 November 2009 / Accepted: 24 March 2010 / Published online: 4 May 2010

Abstract Neuroticism has been linked to a functional polymorphism in the serotonin transporter gene (5-HTTLPR), with short-allele carriers being overrepresented among high-scorers on neuroticism. Studies evaluating neuroticism-related personality traits in relation to the 5-HTTLPR polymorphism among patients with premenstrual dysphoric disorder (PMDD) and are lacking. The primary aim of this study was to evaluate the relationship between PMDD and neuroticism-related personality traits, and secondly, to relate the personality trait scores of PMDD patients to experienced symptom severity and to the 5-HTTLPR short allele. Thirty PMDD patients and 55 asymptomatic healthy controls were included in the study. The Swedish Universities Scale of Personality was used to evaluate personality traits. Genotype analyses were available in 27 PMDD patients and 18 healthy controls. Women with PMDD displayed higher levels of neuroticism-related personality traits (psychic trait anxiety, somatic trait anxiety, embitterment, stress susceptibility and mistrust) than healthy controls, and these effects were most prominent in women with more severe luteal phase symptoms. Furthermore, PMDD patients with at least one copy of the short allele of the 5-HTTLPR polymorphism scored higher on psychic trait anxiety and lack of assertiveness than PMDD patients who were homozygous for the long allele. PMDD patients who suffer from more severe luteal phase symptoms also display increased scores of neuroticism-related personality traits in comparison with healthy controls. Within the group of PMDD patients, differences in certain personality trait scores are associated with the short allele of the 5-HTTLPR polymorphism.

Keywords Personality · Neuroticism · Premenstrual dysphoric disorder · Swedish universities scale of personality · 5-HTTPLPR

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Introduction

The premenstrual dysphoric disorder (PMDD) is characterized by a recurrent cluster of physical and negative mood symptoms during the luteal phase of the menstrual cycle. Although PMDD is generally regarded as an endocrine disorder due to its relation to ovulatory menstrual cycles and progesterone production during the luteal phase (Segebladh et al. 2009; Sundstrom et al. 1999), mounting evidence also indicates that personality, psychosocial, and genetic factors may be important contributors to the syndrome (Ross and Steiner 2003).

Personality traits are characteristic ways of thinking, feeling, and behaving. Once adulthood is reached, personality traits are fairly stable throughout life, and some studies

indicate that certain traits are more stable than others (Caspi et al. 2005; Hampson and Goldberg 2006). Neuroticism for example, defined as an enhanced tendency of experiencing negative emotions such as stress, anxiety and anger, is a stable, heritable personality factor (Lesch et al. 1996) with approximately 50% of the variance accounted for by genetic factors (Canli 2008; Kendler et al. 2006).

The serotonin transporter (5-HTT) is an integral membrane protein which transports the neurotransmitter serotonin from the synaptic cleft into pre-synaptic neurons. A gene-linked polymorphic region (5-HTTLPR) located upstream the 5-HTT transcriptional coding sequence has been reported. The polymorphism consists of insertion or deletion of 43 bp repeated elements which create a short (14 repeat units) or a long (16 repeat units) allele with different transcriptional activities. The short allele has been associated with lower 5-HTTLPR expression levels, resulting in lower serotonin uptake activity compared with the long allele (Heils et al. 1996). In the adult brain, the phenotypic expression of the 5-HTTLPR variants seems to be disappeared, suggesting that the gene variants mainly may regulate fetal development of the serotonergic system and other systems in the CNS (Nordquist and Oreland 2010).

Neuroticism has been linked to the functional polymorphism in the 5-HTTLPR, with the short-allele carriers being overrepresented among high-scorers on neuroticism (Canli and Lesch 2007; Munafo et al. 2006), but non-significant associations have also been reported (Samochowiec et al. 2004). Studies that do not show correlations between neuroticism and 5-HTTLPR are, however, typically based on healthy participants. In populations with major depression or seasonal affective depression, associations between 5-HTTLPR and neuroticism are more commonly reported (Munafo et al. 2006; Praschak-Rieder et al. 2002).

The high expressing variant (L/L) has been associated with psychiatric morbidities such as melancholic depression (Willeit et al. 2003) and postpartum depression (Sanjuan et al. 2008) but also to depressive response to tryptophan depletion (Moreno et al. 2002). Taken together, these studies suggest that being homozygous for either the low or high activity allele might increase sensitivity for the development of mood disorders as compared to being heterozygous. This notion is further supported by studies on affective responses to tryptophan depletion, suggesting that the main effects of 5-HTTLPR polymorphisms on behavior may be present in the homozygous allele-groups, especially in female populations (Brummett et al. 2008; Walderhaug et al. 2007).

The primary aim of this study was to evaluate the relationship between PMDD and personality traits, and secondly, to relate the personality trait scores of PMDD patients to experienced symptom severity and to the 5-HTTLPR short allele. We hypothesized that women with PMDD would display increased scores on the neuroticism-related personality traits in comparison with control subjects. Furthermore, it was hypothesized that more symptomatic PMDD patients and 5-HTTLPR short-allele carriers would display increased scores on the neuroticism-related personality traits in comparison with control subjects and possibly also in comparison with less symptomatic PMDD patients.

Materials and methods

Study population

Thirty PMDD patients and 55 asymptomatic healthy controls were included in the study. Patients were recruited among women seeking help for premenstrual symptoms at the out-patient ward of the Department of Obstetrics and Gynecology, Uppsala University Hospital and from newspaper advertisement.

Included patients met the criteria for PMDD, defined in the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV, 1994). The diagnosis was based on daily, prospective symptom ratings on the cyclicity diagnoser (CD) scale during two cycles prior to inclusion (Sundstrom et al. 1999). The CD scale consists of nine negative mood parameters (depression, decreased interest in usual activities, fatigue, irritability, tension, mood swings, affective lability, difficulties in concentrating and sleep disturbances), two positive mood parameters (cheerfulness and energy), and four somatic symptoms (food cravings, swelling, breast tenderness, and menstrual bleeding). In addition, the CD scale contains a score for measuring every-day social functioning and work performance. The CD scale is a Likert scale ranging from 0–8, with 0 representing a complete absence of a particular symptom, and 8 reflecting the maximal severity of the symptom. Patients were considered to have PMDD if they displayed a 100% increase in the mean ratings of at least five negative symptoms (or a 50% decrease in positive symptoms) during seven premenstrual days compared to seven mid-follicular days, associated with a clinically significant social and occupational impairment. The threshold for impact on daily life was set at a score$\geq$4 for more than two days during the luteal phase (indicating that subjects avoided social interaction during these days). To be included, patients also had to display at least one week of sparse symptoms (scores less than two) in the mid-follicular phase.

Asymptomatic controls were physically healthy women with regular menstrual cycles and no self-report of premenstrual symptoms. Control subjects displayed no significant cyclicity in mental symptoms between the

follicular and luteal phases on the CD scale during two consecutive cycles.

The exclusion criteria for both patients and controls were ongoing treatment with any hormonal compounds, treatment within the last three months with benzodiazepines or other psychotropic drugs including selective serotonin reuptake inhibitors (SSRIs) and presence of any ongoing psychiatric disorder. The presence of psychiatric disorders was evaluated using a structured psychiatric interview, the Swedish version of Mini International Neuropsychiatry Interview (MINI), based on DSM-IV and ICD-10 (Sheehan et al. 1998).

All women gave written informed consent prior to inclusion in the study. The study procedures were in accordance with ethical standards for human experimentation, and the Independent Research Ethics Committee at Uppsala University approved the study.

Personality assessment

Personality assessments were made in the follicular phase. The Swedish universities Scales of Personality (SSP) is a self-rating questionnaire, based on the Karolinska Personality Scales (KSP) (Schalling et al. 1987). Compared to KSP, SSP has a reduced number of items and an improved psychometric quality with better face validity, higher internal consistency and better response differentiation (Gustavsson et al. 2000). The SSP contains 91 items and the participants rated the items on a scale from 1 to 4, where 1 equals "does not apply at all" and 4 equals "applies completely". The items form 13 scales (Table 1). Following factor analysis, these scales are usually grouped into three major factors: Neuroticism-related traits (*Somatic Trait Anxiety*, *Psychic Trait Anxiety*, *Stress Susceptibility*, *Lack of Assertiveness*, *Embitterment*, *Mistrust*), Aggressiveness (*Trait Irritability*, *Verbal Trait Aggression*, *Physical Trait Aggression*, inversed value of *Social Desirability*) and Extraversion (*Impulsiveness*, *Adventure Seeking*, inversed value of *Detachment*) (Gustavsson et al. 2000).

For each scale, the SSP scores are transformed into normative, age-adjusted *T* scores with means of 50 and standard deviations of 10 based on a Swedish gender-stratified non-patient sample (Gustavsson et al. 2000).

5-HTTLPR polymorphism genotype analysis

Blood samples for genotype analyses were available in 27 PMDD patients and 18 healthy controls.

The 5-HTTLPR gene promoter VNTR polymorphism was amplified from 30 ng genomic DNA using the primer sequences: forward 5′-AAC ATG CTC ATT TAA GAA GTG GAA C-3′ and reverse 5′-XCT AGA GGG ACT GAG CTG GAC AAC-3′. The reverse primer was labeled with the fluorescent dye 5′-hex.

PCR was performed in a 10-μl reaction mixture containing 30 ng DNA; 1.0 mM PCR Buffer10×, 1.5 mM $MgCl_2$, 0.2 μM dNTPs; 7%DMSO; 0.8 μM of two primers and 0.5 U Fast Start Taq DNA polymerase (Roche Diagnostics, Germany). The PCR reactions were performed on a GeneAmp 9700 (Applied Biosystems) at the following profile: starting at 94°C for 4 min, followed by 35 cycles of denaturation at 94°C for 45 s, annealing at 61°C for 1 min and elongation at 72°C for 90 s , with final extension at 72°C for 7 min. The PCR products were analyzed by capillary electrophoresis ABI PRISM@3700 DNA Analyzer (Applied Biosystem, USA) and alleles size were determined manually checking on chromatograms using Gene Marker1.5® AFLP/Genotyping software (SoftGenetics LLC®2004. State College, PA, USA). As control material, one third of the sample has been analyzed twice. Errors and inconsistencies have been identified and the genotype analysis was carried out a second time and the PCR products were resolved by electrophoresis on a 2% agarose gel. The gel was run 1 h at 120 V and visualized under UV light. Buffer used as a running buffer was 0.5× Tris–EDTA-Buffer (TEB) and sizes were determined by comparison with a 100 bp DNA sequencing ladder.

Statistical analyses

The study had an 80% power to detect a mean difference of 5.0 *T* scores (equal to half a standard deviation) between

Table 1 Demographic variables and physical characteristics of the PMDD patients and the control subjects

	PMDD patients (n=30)	Control subjects (n=55)	p value
Age	33.2±8.9	26.2±4.5	0.001
Height	168±13	168±6	ns
Weight	64.0±13.4	61.6±10.3	ns
Caucasian origin	28 (93.3%)	55 (100.0%)	ns
College/university education	20 (66.7%)	37 (67.3%)	ns
Married/cohabiting	16 (53.3%)	18 (32.7%)	0.05
Parous subjects	14 (46.7%)	5 (9.1%)	0.001
Smokers	1 (3.3%)	1 (1.8%)	ns

PMDD patients and controls, given a standard deviation of 8.0. Continuous variables were compared using independent *t* tests and are presented as mean ± SD. Skewed data was log-transformed prior to analyses. For evaluation of the influence of symptom severity on the personality trait scores one-way ANOVA followed by Tukey's post hoc tests was used. Analyses of differences in allele frequency were performed using chi-square.

Because of the sociodemographic differences between PMDD patients and control subjects, the personality trait scores were also compared between groups by multivariate linear regression with adjustment for parity and civil status.

To enable comparison of PMDD symptom severity between individuals, a method developed by Wang and co-workers was used (Wang et al. 1996) in which the number of expressed negative mood symptoms per day during the premenstrual period defines high- and low-severity PMDD patients. The CD-scale ratings of the first diagnostic cycle were used and the total number of days with expressed symptoms (symptom score≥2) in the 10-day premenstrual period was counted for each of the four core symptoms of PMDD (irritability, depression, anxiety, and mood swings). A day with scores for negative symptoms ranging between 0 and 1 was defined as symptom-free. This procedure resulted in a scale of symptom severity ranging from 0 to 40. Based on a median split (27.5), the PMDD patients were divided into two equally large groups, a high-severity group (n=15) and a low-severity group (n=15).

Based on prior research (Munafo et al. 2006), analyses of the 5-HTTLPR genotype influence on personality trait scores in PMDD patients were made by comparing short-allele carriers (S/S and S/L) with homozygous carriers of the long allele (L/L). For further analyses on 5-HTTLPR genotype, PMDD patients and healthy controls were grouped as homozygotes (S/S and L/L) and heterozygotes (S/L).

All statistical analyses were performed with SPSS 15.0. A two-sided p value less than 0.05 was considered significant.

Results

Demographic factors

The control subjects were slightly younger, had fewer children and were also less likely to be cohabiting/married than the PMDD patients. Otherwise, there were no significant socio-economic differences between groups (Table 1).

Symptom severity

The high-severity group did not differ from the low-severity group regarding summarized negative mood scores on the CD scale (i.e. symptom scores of depression, anxiety, mood swings, and irritability) during the follicular phase of the menstrual cycle but displayed higher summarized negative mood scores in the luteal phase (group × phase interaction $F(1,28)=43.46$; $p<0.001$).

Personality traits

PMDD patients scored significantly higher on somatic trait anxiety, psychic trait anxiety, embitterment, trait irritability, mistrust, and detachment compared to healthy control subjects (Table 2). Following adjustment for parity and civil status, PMDD patients also displayed increased scores for stress susceptibility and decreased scores for social desirability in comparison with control subjects (Table 2). The differences in personality trait scores between PMDD patients and healthy controls were mainly driven by most symptomatic PMDD patients. When high-severity and low-severity PMDD patients were evaluated separately in comparison to control subjects, it was primarily the high-severity PMDD patients who displayed significant increases in personality trait scores in comparison with the control subjects. High-severity PMDD patients had higher scores on somatic trait anxiety, psychic trait anxiety, embitterment and mistrust as compared to control subjects (Table 3), whereas low-severity PMDD patients only scored higher on the detachment scale than control subjects. Following adjustment for parity and civil status, high-severity PMDD patients also displayed higher scores for stress susceptibility and trait irritability in comparison with control subjects and low-severity PMDD patients also displayed higher scores of mistrust (Table 3). However, no differences between high- and low-severity PMDD patients were detected.

5-HTTLPR polymorphism genotype

5-HTTLPR genotype was completed in 27 PMDD patients and 18 control subjects. Allele frequencies fell within expected ranges, based on multiple published reports for Caucasians. For the healthy controls, the frequency of the long allele was 0.56 and of the short allele was 0.44, resulting in Hardy–Weinberg equilibrium (HWE; $x^2=2.21$; $p=0.14$). Corresponding allele frequencies for PMDD patients were 0.59 of the long allele and 0.41 for the short allele with HWE ($x^2=1.47$; $p=0.23$).

There was a trend that homozygous allele carriers (S/S and L/L) were more common among PMDD patients ($p<0.051$). Ten (37.0%) PMDD patients were heterozygotes and 17 (63.0%) were homozygotes (S/S, 6 (22.2%); L/L, 11 (40.7%)), whereas the corresponding figures in control subjects were 12 (66.7%) heterozygotes and six (33.3%) homozygotes (S/S, 2 (11.1%); L/L, 4 (22.2%)).

Table 2 Mean ± standard deviation of personality trait *T* scores on the Swedish universities scale of personality for PMDD patients and control subjects

SSP subscales	PMDD patients (n=30)	Control subjects (n=55)	Unadjusted p value	Adjusted p value[a]
Somatic trait anxiety	52.3±9.0	45.7±6.8	0.001	0.001
Psychic trait anxiety	51.0±9.1	46.5±7.3	0.014	0.003
Embitterment	49.1±10.4	44.5±6.7	0.034	0.002
Stress susceptibility	53.5±11.0	48.8±10.3	0.051	0.001
Mistrust (logarithmic)	50.5±10.8	42.2±8.4	0.001	0.001
Lack of assertiveness	49.1±9.7	48.9±8.0	0.91	0.35
Trait irritability	53.6±12.4	47.5±10.2	0.016	0.005
Verbal trait aggression	49.2±10.3	47.6±8.7	0.48	0.075
Physical trait aggression (logarithmic)	45.8±10.3	41.8±7.1	0.073	0.077
Social desirability	49.6±7.3	51.0±8.8	0.48	0.022
Impulsiveness	50.4±9.9	47.0±8.2	0.09	0.09
Adventure seeking	49.4±10.0	50.2±8.0	0.69	0.86
Detachment	49.6±7.8	44.8±8.0	0.009	0.01

[a] Adjusted for parity and civil status

Within the PMDD patients, short-allele carriers displayed higher scores on psychic trait anxiety (presence of short 54.0±6.9 vs. L/L 46.0±10.8, p<0.05) and lack of assertiveness (presence of short 53.0±6.8 vs. L/L 42.5±9.8, p<0.01). Because of the low frequency of homozygous carriers of the long allele among control subjects, comparisons of personality trait scores were not performed with this group.

Discussion

The main finding of the present study was that PMDD patients displayed increased scores of psychic trait anxiety, somatic trait anxiety, embitterment, stress susceptibility, and mistrust compared to control subjects. These traits, together with lack of assertiveness, are considered to belong to the domain of neuroticism-related personality traits in the SSP

Table 3 Mean ± standard deviation of personality trait *T* scores on the Swedish universities scale of personality for high- and low-severity PMDD patients and control subjects

SSP subscales	PMDD high-severity (n=15)	PMDD low-severity (n=15)	Control subjects (n=55)
Somatic trait anxiety	55.1±9.4[a]	49.5±7.8	45.7±6.8
Psychic trait anxiety	52.1±9.9[b]	50.0±8.4	46.5±7.3
Embitterment	51.9±11.0[c]	46.3±9.3	44.5±6.7
Stress susceptibility	54.9±12.2[d]	52.2±9.9	48.8±10.3
Mistrust (logarithmic)	52.4±12.2[a]	48.5±9.2[d]	42.2±8.4
Lack of assertiveness	49.2±11.0	49.0±8.5	48.9±8.0
Trait irritability	54.2±11.8[d]	53.0±13.5	47.5±10.2
Verbal trait aggression	50.8±9.2	47.5±11.4	47.6±8.7
Physical trait aggression (logarithmic)	45.6±8.7	46.1±12.0	41.8±7.1
Social desirability	48.2±8.7	51.0±5.6	51.0±8.8
Impulsiveness	52.0±7.2	48.9±9.2	47.0±8.2
Adventure seeking	49.6±10.9	49.2±9.4	50.2±8.0
Detachment	48.8±9.3	50.4±6.2[b]	44.8±8.0

There were no significant differences in personality trait scores between high- and low-severity PMDD patients

[a] Significantly different from control subjects, p<0.001, one-way ANOVA with post hoc Tukey HSD

[b] Significantly different from control subjects, p<0.05, one-way ANOVA with post hoc Tukey HSD

[c] Significantly different from control subjects, p<0.01, one-way ANOVA with post hoc Tukey HSD

[d] Significantly different from controls, p<0.05–0.01, linear regression with adjustment for parity and civil status

(Gustavsson et al. 2000). Furthermore, our results indicated that the differences in personality trait scores between PMDD patients and control subjects were mainly driven by the most symptomatic PMDD patients, as only one of the neuroticism-related personality trait scores was different between low-severity patients and control subjects. These findings could implicate that certain personality traits are related to, not only the development of PMDD, but also the severity of the disorder, a relationship also reported by Freeman et al. (1995).

Clearly, our findings must been interpreted in the light of the relatively low power of the study and the fact that no correction for multiple comparisons was made. Besides the neuroticism-related personality trait scores, a larger sample size could possibly have been able to find differences between PMDD patients and controls in the aggressiveness scores as well. Furthermore, the non-significant differences in personality trait scores between high- and low-severity PMDD patients may also reflect the relatively modest sample size.

Research in PMDD and personality is limited and many studies have relied on retrospective ratings by participants for the premenstrual syndrome/PMDD diagnosis, a method that not only gives a general exaggeration of reported symptoms, but also has been shown to especially bias individuals with neuroticism-related personality traits to overestimate their symptoms (Taylor et al. 1991). However, more recent studies, based on prospective ratings, have indicated that certain personality traits can be associated to PMDD. Critchlow et al. (2001) found a higher degree of obsessive–compulsive traits in PMDD patients than in healthy controls, and Freeman et al. (1995) reported that PMDD patients had increased scores on harm avoidance, novelty seeking, and slightly higher scores on reward dependence in comparison to a normal population. The differences in personality trait scores between the PMDD patients and the healthy controls in the present study were small and are thus more likely to reflect variations within the normal spectra rather than actual personality disorders. This would be in line with the study of Critchlow et al. (2001) who investigated the prevalence of personality disorders and did not report a higher prevalence in PMDD patients than in healthy controls.

PMDD patients who carried the short allele for 5-HTTLPR displayed increased scores of psychic trait anxiety and lack of assertiveness in comparison with PMDD patients who were homozygous carriers of the long allele. This finding is in line with previous research indicating that neurotic personality traits are related to the short allele of the serotonin transporter gene (Canli 2008; Lesch et al. 1996). Taken together, genetic vulnerability factors and associated personality traits may, in concert or separately, influence symptom severity in PMDD patients. As both these factors, and especially genetic vulnerability factors, are associated with major depression (Enns and Cox 1997; Kendler et al. 2006; Ramklint and Ekselius 2003), our results may also suggest that highly symptomatic PMDD patients (with elevated neuroticism-related personality trait scores) may be more prone to develop major depression. However, whether PMDD patients with high scores on neuroticism-related personality traits and/or genetic vulnerability factors are particularly susceptible for future development of depression remains to be evaluated in longitudinal studies.

There was a trend that PMDD patients more often were carriers of the homozygous alleles for 5-HTTLPR than control subjects. However, because of the limited sample size and prior negative findings in terms of allelic distribution profiles in PMDD patients (Magnay et al. 2006), these data need confirmation in larger cohorts before any interpretations can be made.

In conclusion, the present study indicates that PMDD patients have higher scores of neuroticism-related traits than healthy controls and this finding was mainly driven by the most symptomatic patients. Moreover, PMDD patients who carried the short allele for 5-HTTLPR displayed increased scores of psychic trait anxiety and lack of assertiveness in comparison with PMDD patients who were homozygous carriers of the long allele. The differences in neuroticism-related personality traits between PMDD patients and healthy controls and the differences in personality traits scores due to variable genetic vulnerability within the PMDD group might support the fact that the development and severity of PMDD is related to neurobiological risk factors and that those risk factors might be similar to the mechanisms underlying major depression. Clearly, further studies elucidating the interactions between personality factors and genetic susceptibility in larger samples of PMDD patients are warranted.

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