

## **Serotonin, personality and borderline personality disorder**

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### **Abstract**

Serotonin is one of the neurotransmitters implicated in normal personality. Many psychobiological models of personality include some dimensions related to serotonin. For instance, the harm avoidance dimension of the biosocial model developed by Cloninger is related to serotonergic activity. Higher scores on the harm avoidance dimension should theoretically reflect increased serotonergic activity. However, correlation studies related serotonin activity to harm avoidance dimension have not yielded consistent findings. These controversial results are probably related to the complexity of the neurotransmitter systems, and the different assessment techniques used in these studies. Finally, recent genetic studies have examined the association between personality dimensions and serotonergic receptor polymorphisms with mixed results. Serotonin is not only related to some dimensions of normal personality. Several psychopathological disorders are associated with serotonergic dysfunction. More particularly, borderline personality disorder (BPD) can be defined by many of the symptoms associated with serotonergic dysregulation, including affective lability, suicidal behaviours, impulsivity and loss of impulse control. Indeed, several reports have demonstrated the efficacy of selective serotonin re-uptake drugs in treating the depressive and impulsive symptoms of patients with BPD. Moreover, some challenge studies have reported a lower serotonergic activity in BPD. Because these challenges are not specific, we have assessed the serotonergic activity in BPD with the flesinoxan challenge. Preliminary results showed that the prolactin responses to flesinoxan were significantly lower in BPD patients compared to those observed in controls.

**Keywords:** serotonin; personality; borderline personality disorder

### **Introduction**

Serotonin is one of the neurotransmitters implicated in normal personality. Many psychobiological models of personality include some dimensions related to serotonin. For instance, in the Zuckerman model of personality (1), the dimension of impulsive unsocialized sensation seeking (ImpUSS) is negatively correlated with serotonergic dimension. Again, the harm avoidance dimension of the biosocial model developed by Cloninger (2) is related to serotonergic activity. Serotonin is not only related to some dimensions of normal personality. Several psychopathological disorders are associated with serotonergic dysfunction. More particularly, borderline personality disorder (BPD) can be defined by many of the symptoms associated with serotonergic dysregulation, including affective lability, suicidal behaviours, impulsivity and loss of impulse control. This review presents some recent findings on serotonin, personality and BPD. More particularly, this review focuses on the biosocial model of Cloninger and on the flesinoxan challenge test.

### **Serotonin and personality**

Cloninger and colleagues have proposed a biosocial model of personality based on four temperaments (novelty seeking, harm avoidance, reward dependence and persistence) and three characters (self-directedness, cooperativeness and self-transcendence) (3). Novelty seeking is defined as the tendency to respond actively to novel stimuli leading to pursuit of rewards and escape from punishment. Harm avoidance corresponds to the tendency toward an inhibitory response to signals of aversive stimuli that lead to avoidance of punishment and non-reward. Reward dependence is defined as the tendency for a positive response to signals of reward to maintain or resist behavioural extinction. Persistence is described in terms of perseverance despite frustration and fatigue. Self-directedness refers to the ability of an individual to control, regulate and adapt his behaviour to fit the situation in accord with individually chosen goals and values. Cooperativeness is formulated to account for individual differences in identification with and acceptance of other people. Self-transcendence is a characteristic associated with spirituality, and refers generally to identification with everything conceived as essential and consequential parts of a unified whole. The temperament and character inventory (TCI) is a 226-item self-questionnaire developed by Cloninger and colleagues to assess the seven dimensions of personality (4).

According to this model, three of the four temperaments were associated with a specific central neurotransmitter. Novelty seeking was theoretically associated to dopaminergic activity; harm avoidance to serotonergic activity; and reward dependence to noradrenergic activity. More particularly, higher scores on the harm avoidance dimension should theoretically reflect increased serotonergic activity. This is directly supported by the fact that an inverse relationship was noted between aggression and harm avoidance, as well as between aggression and central 5-HT functioning (5,6).

The relationship between harm avoidance and serotonergic activity has been evaluated in several studies. Pfohl et al. (7) have described a higher score of the harm avoidance dimension in obsessive-compulsive disorder (OCD) patients compared to controls, but without any association between this dimension and platelet imipramine binding. In another study, the score of the harm avoidance dimension was higher in a group of bulimic women compared to normal women, but the whole blood serotonin levels were not related to this dimension (8). In the study by Limson et al. (9) there were no significant correlations between cerebrospinal fluid concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid and harm avoidance scores. However, given the complexity of the neurotransmitter systems, these studies cannot be considered as evidence against a relationship between serotonergic activity and the harm avoidance dimension. In contrast, Nelson and Cloninger (10) have demonstrated that harm avoidance and reward dependence scores were found to significantly predict the response to the 5-HT<sub>2</sub> receptor antagonist and 5-HT reuptake inhibitor antidepressant nefazodone in depressed patients. More recently, Gerra et al. (11) found that harm avoidance scores correlated significantly with prolactin (PRL) response to d-fenfluramine in healthy volunteers.

Recently, our group has developed a serotonergic challenge test using flesinoxan (12). Flesinoxan is a highly potent and selective 5-HT<sub>1A</sub> agonist inducing a significant and dose-dependent release of PRL and Cortisol in normal subjects. In contrast, depressed patients exhibited a blunted Cortisol response, and more particularly those with a history of suicide attempts. Flesinoxan challenge was a good candidate to assess the relationship between harm avoidance and serotonergic activity. In a first study (13), we have reported a positive association between the PRL response to flesinoxan and the harm avoidance dimension in a group of depressed patients. This result appears consistent in light of the studies noted above. However, a major pitfall of this study was the state dependence of harm avoidance dimension in depression. Indeed, as harm avoidance has been shown in this and other studies (14,15) to correlate with the severity of depression, the positive relationship between harm avoidance and the PRL response to flesinoxan could be due to the depressive status. Therefore, the same design has been carried out in a sample of non-depressed subjects (16). This second study ostensibly replicates and extends the first one (13) and is consistent with the results of Gerra et al. (11)

However, an important limitation of these studies is the selective effect of flesinoxan on the 5-HT<sub>1A</sub> receptors. Indeed, the pharmacologically induced PRL response to flesinoxan is an indirect index of serotonergic neurotransmission and could involve areas of the brain not related with the neural substrate of harm avoidance hypothesized by Cloninger. Moreover, the lack of a placebo-controlled flesinoxan challenge limits the conclusions of this study. Therefore, to examine exhaustively the hypothesized link between harm avoidance and serotonergic activity, future studies should be conducted using agonist and antagonist serotonergic agents in non-patient groups.

The association between serotonergic function and harm avoidance dimension of the Cloninger model was also investigated using genetic markers. Indeed, recent genetic studies have examined the association between personality dimensions and serotonergic receptor polymorphisms with mixed results. No association was observed between individuals grouped by the long and short forms of the serotonin transporter gene and the personality dimension of harm avoidance (17). In contrast, an association between harm avoidance and the short form of the serotonin transporter gene (5-HTTLPR) has been reported in another study (18). In a recent study, no contribution of the 5-HT<sub>2a</sub> polymorphism on harm avoidance personality trait emerged (19).

## **Serotonin and BPD**

BPD is defined in DSM-IV (20) as 'a pattern of instability in interpersonal relationships, self-image, and affects, and marked impulsivity'. The syndrome of BPD may be classified into four groups of symptoms: affective, impulsive, ego/interpersonal and psychotic. Several of these symptoms are associated with serotonergic dysfunction, and more particularly affective lability, suicidal behaviours and impulsive aggression. Based on this statement, serotonin uptake inhibitors were studied openly in BPD patients soon after the release of fluoxetine. Three reports have demonstrated the efficacy of fluoxetine in treating the depressive and impulsive symptoms of patients with BPD (21-23). However, these studies were not double-blind, which could lead to bias in collecting the data. The first double-blind, placebo-controlled study conducted among a small group of BPD patients

demonstrated clear efficacy for fluoxetine over placebo along a number of dimensions, including depression, anxiety and global function (24). The second controlled fluoxetine study among BPD patients reported improvement in a number of symptoms, but this improvement was not statistically significant, except for aggression against objects (25). In another controlled trial in 40 out-patients with personality disorders including 13 with BPD, fluoxetine had an anti-aggressive effect on impulsive aggressive individuals with personality disorder including BPD (26). In an open trial with sertraline, significant reduction in irritability and aggression were reported in BPD (27). Significant improvement of BPD patients was also reported with venlafaxine (28). However, more controlled trials with larger patient populations are necessary to replicate these results.

Platelet studies have been carried out in BPD to assess the serotonergic function in this disorder. Platelet 5-HT was higher in patients with BPD than in non-borderline patients and normal controls, and was positively correlated with the disposition to experience anger (29,30).

Another way to assess further the role of the 5-HT function in BPD is the use of specific pharmacological probes. Coccaro et al. (5) administered the non-specific 5-HT releaser/reuptake blocker fenfluramine to patients with major depressive disorders and/or personality disorders including BPD and found that PRL response was blunted compared to non-borderline personality disorder and normal control subjects, independent of the comorbidity of major affective disorder. Moreover, PRL response was negatively correlated with impulsive aggression and with history of suicide attempts. In contrast, Martial et al. [31] have reported higher PRL response and lower Cortisol response to fenfluramine in five BPD women compared to controls. Recently, Soloff et al. (32) performed a study using positron-emission tomography (PET) during a fenfluramine challenge test in BPD. The results shown that patients with BPD have lower responses to serotonergic stimulation in areas of prefrontal cortex, a region associated with regulation of impulsive behaviour. Hollander et al. (33) found higher Cortisol levels and marginally blunted PRL response to the partial 5-HT agonist meta-chlorophenylpiperazine (m-CPP) in eight male patients with BPD compared to controls. However, the results among women (four subjects) are not significant. This gender difference, as noted by the authors, might be attributable to circulating ovarian hormones. The authors also reported that m-CPP induced a distinctive spacy (depersonalized/dealized) and high (euphoric) behavioural reaction in the patients. The same group found in a larger sample of BPD patients a significant association between the presence of a spacy and high behavioural response to m-CPP and increased PRL and Cortisol peak on m-CPP challenge (34). In another study with m-CPP, women with a BPD diagnosis had PRL and Cortisol blunted responses to this challenge (35). Furthermore, these authors reported a significant negative correlation between delta peak PRL values and abuse characteristics, such as the severity and duration of physical and sexual abuse. They concluded that the alteration of the serotonergic system was probably not related to the BPD diagnosis *per se*, but to sustained traumatization during childhood.

Since these challenges are not specific, we have assessed the serotonergic activity in BPD with the flesinoxan challenge test. This preliminary study was conducted among 20 BPD patients (14 women) with a mean age of 30.5 years (SD = 10.2) and 20 healthy volunteers matched for gender with a mean age of 37.9 years (SD = 9.6). The age difference between the two groups was significant ( $Z = -2.27$ ,  $P = 0.02$ ). The diagnosis of BPD was based on the DSM-IV criteria and on the self-questionnaire from the Structured Clinical Interview for DSM-III Axis II (SCID-II). According the DSM-IV criteria, 16 BPD patients had a current diagnosis of major depressive disorder, and four had an eating disorder. The patients were free of medication at least 2 weeks before the challenge. Because of the influence of oestrogen on the prolactin levels during the menstrual cycle, the flesinoxan challenge test was performed between the third and the 12th day of the menstrual cycle. The Ethical Committee of the University of Liege Medical School approved the protocol and all subjects gave their informed consent. There was a significant difference between BPD patients ( $40627 \pm 21042$  mIU min/mL) and healthy volunteers ( $75546 \pm 46612$  mIU min/mL) for PRL response to flesinoxan ( $Z = -2.92$ ,  $P = 0.003$ ). Among the BPD patients, PRL response to flesinoxan was lower in patients with past history of suicide attempts ( $N = 8$ ) compared to patients with a negative history ( $P = -3.04$ ,  $P < 0.002$ ). Because flesinoxan stimulates specifically the 5-HT<sub>1A</sub> postsynaptic receptors, these results suggest that BPD patients are characterized by lower 5-HT<sub>1A</sub> receptor sensitivity. Overall, this study is consistent with previous studies that have reported lower PRL response to serotonergic challenge tests. Some limitations of the study should be acknowledged. First, the lack of a placebo-controlled flesinoxan challenge limits the conclusions of this study. Another important limitation of this study is the use of a self-report questionnaire to assess Axis II diagnoses. Given the complexity of personality pathology, a structured interview schedule would have been preferable. The comorbidity between Axis II and Axis I diagnostic limits also the conclusions. The PRL blunted response observed among BPD patients could be due to the comorbidity on Axis I, and more particularly with major depressive disorder. However, some studies have reported that PRL response to flesinoxan did not differ between depressed patients and controls, but that PRL response was lower in a subgroup of depressed patients characterized by past suicidal history (36). A final limitation is the lack of behavioural assessment for impulsivity, irritability.

## Conclusions

Taken together, the data reported above support the implication of serotonin in both normal and disordered personality. More specifically, serotonergic activity is related with the harm avoidance dimension of the model developed by Cloninger. However, some results are not consistent with this relationship. This may indicate that the relation between serotonin and harm avoidance is indirect, with the contribution of other neurotransmitter systems. An alternative hypothesis is the heterogeneity of the subjects included in these studies and the different tolls for serotonin assessment. Concerning BPD, the results reported here show a major implication of the serotonergic function in the aetiology of this disorder and are consistent with previous studies which linked lower serotonergic activity and impulsivity. These findings provide interesting track for the pharmacological treatment of this dramatic disorder. However, more controlled studies with larger patients populations are necessary to replicate the results of existing research.

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