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ORIGINAL RESEARCH

Impulsivity, gender, and the platelet serotonin transporter in healthy subjects

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Abstract: The present study explored the possible relationships between impulsivity, gender, and a peripheral serotonergic marker, the platelet serotonin (5-HT) transporter (SERT), in a group of 32 healthy subjects. The impulsivity was measured by means of the Barratt Impulsivity Scale, version 11 (BIS-11), a widely used self-report questionnaire, and the platelet SERT was evaluated by means of the specific binding of ^{3}H-paroxetine (^{3}H-Par) to platelet membranes, according to standardized protocols. The results showed that women had a higher BIS-11 total score than men, and also higher scores of two factors of the same scale: the motor impulsivity and the cognitive complexity. The analysis of the correlations revealed that the density of the SERT proteins, as measured by the maximum binding capacity (B_{max}) of ^{3}H-Par, was significantly and positively related to the cognitive complexity factor, but only in men. Men showed also a significant and negative correlation with the dissociation constant, Kd, of (^{3}H-Par) binding, and the motor impulsivity factor. These findings suggest that women are generally more impulsive than men, but that the 5-HT system is more involved in the impulsivity of men than in that of women.

Keywords: impulsivity, gender, serotonin transporter, Barratt Impulsivity Scale, platelets, ^{3}H-paroxetine

Introduction

The brain serotonin (5-HT) system plays an important role in the modulation of different functions and behaviors including appetite, sleep, memory and learning, mood, sexuality.[1,2] However, on the basis of a wealth of preclinical and clinical observations,[3–8] one of the most intriguing suggestions regarding the general role of 5-HT in the central nervous system (CNS) is that it might serve as a "modulator" of impulsivity and aggression.[9–13]

Several studies, employing different means to reduce the functionality of 5-HT, generally led to increased aggressive behaviors in animal models.[14,15] In humans, autopsies carried out on suicide cases revealed abnormalities of different serotonergic parameters, such as decreased 5-HT levels,[16,17] increased and reduced density of 5-HT2A and 5-HT1A receptors, respectively.[17,18] Furthermore, a localized reduction of the 5-HT transporter (SERT) binding in the ventral prefrontal cortex, or fewer SERT mRNA expressing neurons were detected in the dorsal raphe nuclei of suicide victims, as compared with individuals with other disorders.[16,19,20]

Reduced concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of 5-HT, have been reported in the cerebrospinal fluid (CSF) of violent suicide attempters[21,22] and especially in those who had committed it by violent means.[23]

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The link between reduced CSF 5-HIAA and aggression has been subsequently supported by the observation of an inverse relationship with measures of impulsive aggression in male personality-disordered subjects,[24,25] male violent offenders,[3] or alcoholics.[26,27] A similar relationship has been demonstrated between hormonal responses to acute serotonergic challenges and measures of impulsive aggression in personality-disordered subjects[28–34] or healthy volunteers.[35–38]

In spite of these intriguing suggestions, a direct evidence of a link between the serotonergic system and impulsivity is still lacking, especially in healthy subjects. This is also due to intrinsic problems of research on this topic: first, the definition of impulsivity, for which no general agreement exists. An exhaustive definition is that given by the International Society for Research on Impulsivity (ISRI), which considers it as "a human behavior without adequate thought, the tendency to act with less forethought than do most individuals of equal ability and knowledge, or a predisposition toward rapid, unplanned reactions to internal or external stimuli without regard to negative consequences of these reactions". Second, the assessment of impulsivity, which might permit to compare different studies. One of the most used and validated instruments is the so-called "Barratt Impulsivity Scale", which is the results of decades of efforts and modifications until the latest version 11 (BIS-11)[39] and considers impulsivity as a trait influenced by temperament and, as such, heritable and widely distributed in the population.[40,41] Third, the availability of peripheral models of the serotonergic system, which should be reliable, easy to obtain, relatively safe and to be applied routinely in large samples. The SERT present in platelets fulfills all these requirements, especially after the demonstration of its identity with the same structure expressed in the CNS.[42,43] A reduced density of platelet SERT was reported in individuals with personality disorders and aggressive behavior and in suicide attempters.[44,45] Others[46] reported a relationship between the short variant of the SERT promoter polymorphism (*SLC6A4*C*), a blunted fenfluramine-induced prolactin release and aggressive impulsivity, in a group of abstinent alcoholic patients and healthy volunteers, while suggesting that this genotype would contribute to altered serotonergic regulation of emotions. Previously, the same polymorphism was found to be linked to the two anxiety-related sub-dimensions of harm avoidance,[47] and to increased neuroticism (which includes impulsivity) on a personality inventory and decreased agreeableness in general population samples.[48,49]

Given the paucity of available information, therefore, the aim of this study was to explore and compare impulsivity in a group of healthy individuals of both sexes, as well as to investigate the possible relationships between the platelet SERT and impulsivity characteristics. The platelet SERT was evaluated by means of the specific binding of ^{3}H-paroxetine (^{3}H-Par), one of the most selective ligands to label it, and impulsivity was assessed by means of the BIS-11 questionnaire.

Materials and methods
Subjects

Thirty-two drug-free volunteers of both sexes (15 men and 17 women, aged between 27 and 51 years, mean ± standard deviation [SD]: 36 ± 7) were included in the study. They had no family or personal history of any major psychiatric disorder, as assessed by a psychiatric interview, carried out by a senior psychiatrist (DM) by means of the SCID.[50] They were recruited amongst medical and nursing staff at the Dipartimento di Psichiatria, Neurobiologia, Farmacologia e Biotecnologie, University of Pisa, Italy. All subjects were free of any physical illness, as documented by a general check-up and by the normal blood and urine tests. All were psychotropic drug-free, none were heavy smokers or belonged to HIV-risk groups. They all gave their informed written consent to participate in the study, which was approved by the Ethics Committee of Pisa University.

Impulsivity assessment

The impulsivity was assessed by means of the BIS-11 questionnaire validated into Italian.[51]

The BIS-11 is a self-report scale developed to measure impulsivity as a stable characteristic, composed by 30 items, which are answered on a four-point scale; items are scored 1, 2, 3, 4 where 4 indicates the most impulsive response: the higher the total scores for all items, the higher the level of impulsivity. The total score ranges between 30 and 120, with no established cut-off point and is the result of the sum of three different subscales: attentional (rapid shifts of attention and impatience with complexity), motor (impetuous action), and nonplanning (lack of future orientation) impulsivity. In addition, the 30 items form six factors determined by principal component analyses: attention, motor impulsivity, self-control, cognitive complexity, perseverance, and cognitive instability.

Preparation of platelet membranes and ^{3}H-Par binding assay

Twenty-five ml of blood was withdrawn from fasting subjects between 8:00 and 9:00 am in the months of January and February to avoid circadian or seasonal rhythms, into plastic

tubes containing 5 mL of anticoagulant (sodium citrate, 2.2%, and citric acid, 1.2%). Platelet-rich plasma was obtained by low-speed centrifugation (1,500 g for 15 min at 23°C). Platelets were precipitated from platelet-rich plasma by centrifugation at 1500 g for 15 min at 23°C and then stored at −80°C until assay, which was performed within one week. At the time of assay, platelets were washed in 10 mL of ice-cold 50 mmol/L Tris-HCl buffer (pH 7.4) and were centrifuged at 10,000 g for 10 min at 4°C. The resulting pellet was homogenized by an Ultraturrax homogenizer in 10 volumes of 5 mmol/L Tris-HCl buffer (pH 7.4) and were centrifuged at 30,000 g for 10 min at 4°C. The supernatant was discarded, and the final membrane pellet was re-suspended in the assay buffer (50 mmol/L Tris-HCl, 120 mmol/L NaCl and 5 mmol/L KCl, pH 7.4), and homogenized by an Ultraturrax homogenizer. The binding of ^{3}H-Par to SERT on platelet membranes was determined according to the method of Marazziti and colleagues.[52] The ^{3}H-Par binding assays were performed in an incubation mixture consisting of 100 µL of platelet membranes (50–100 µg protein/tube), 50 µl of ^{3}H-Par (Perkin-Elmer, Life Science, Milan, Italy; specific activity: 15.5 Ci/mmol) at concentrations ranging between 0.4 and 40 nmol/L, and 1850 µL of assay buffer. Specific binding was estimated as the binding remaining in the presence of 10 µmol/L fluoxetine (kindly provided by Eli-Lilly, Indianapolis, IN), used as the unlabeled competitor for SERT binding site. All samples were assayed in duplicate and incubated at 22°C for one hour. The reaction was then halted by adding 5 mL of cold assay buffer, followed by immediate filtration under vacuum through glass fiber filters GF/C (Whatman International, Maidstone, UK).

The filters were washed three times with 5 mL of the assay buffer and dried, and the SERT-bound radioactivity trapped on the filters was counted in 4 mL of scintillation fluid by a scintillation spectrometry counter 1600 TR (Packard Bioscience, Groningen, The Netherlands). Protein concentration was determined according to the method of Lowry, as modified by Peterson.[53]

Statistical analyses

Equilibrium-saturation binding data, the maximum binding capacity (B_{max}, fmol/mg protein) and the dissociation constant (Kd, nM) were analyzed by means of iterative curve-fitting computer programmes EBDA [Biosoft, Cambridge, UK].

The differences in binding parameters or BIS total or subscale scores between women and men were analyzed by means of the Student's t-test.

The possible effects of age and sex on biological parameters were investigated by means of the analysis of covariance, while the correlations between variables were explored using the Pearson method, all with SPSS software (version 12.1; SPSS Inc, Chicago, IL, USA).

Results

The B_{max} (mean ± SD, fmol/mg protein) and Kd (mean ± SD, nM) values were 1135 ± 119 and 0.095 ± 0.02, with no difference between women and men (Table 1). The BIS total score in all subjects was 55.1 ± 5.92, significantly higher in women than in men (58.76 ± 6.9 vs. 51.45 ± 4.94, t = −3.034, P = 0.005). In addition, the following factor scores were also higher in women than in men: motor impulsivity

Table 1 ^{3}H-Par binding parameters (B_{max}, mean ± SD, fmol/mg prot.; Kd, mean ± SD, nM) and BIS-11 total, subscale and factor scores (mean ± SD) in men and women

		Men	**Women**
^{3}H-Par binding parameters	B_{max}	1135 ± 127	1137 ± 111
	Kd	0.094 ± 0.02	0.096 ± 0.03
BIS-11 total score		51.45 ± 4.94	58.76 ± 6.9*
BIS-11 subscale	Attentional	18.36 ± 2.87	20.29 ± 2.86
	Motor	17.18 ± 1.72	21.17 ± 2.89
	Nonplanning	15.9 ± 1.86	17.29 ± 3.78
BIS-11 factor	Attention	7.09 ± 1.3	7.76 ± 2.35
	Motor impulsivity	11.54 ± 2.06	14.7 ± 3.05**
	Self-control	11.18 ± 2.08	12.58 ± 3.1
	Cognitive complexity	11.27 ± 1.79	12.52 ± 1.37***
	Perseverance	5.63 ± 1.12	6.47 ± 1.12
	Cognitive instability	4.72 ± 1.27	4.7 ± 1.44

Notes: *Significant: t = −3.034, P = 0.005; **significant: t = −3.004, P = 0.006; ***significant: t = −2.096, P = 0.046.
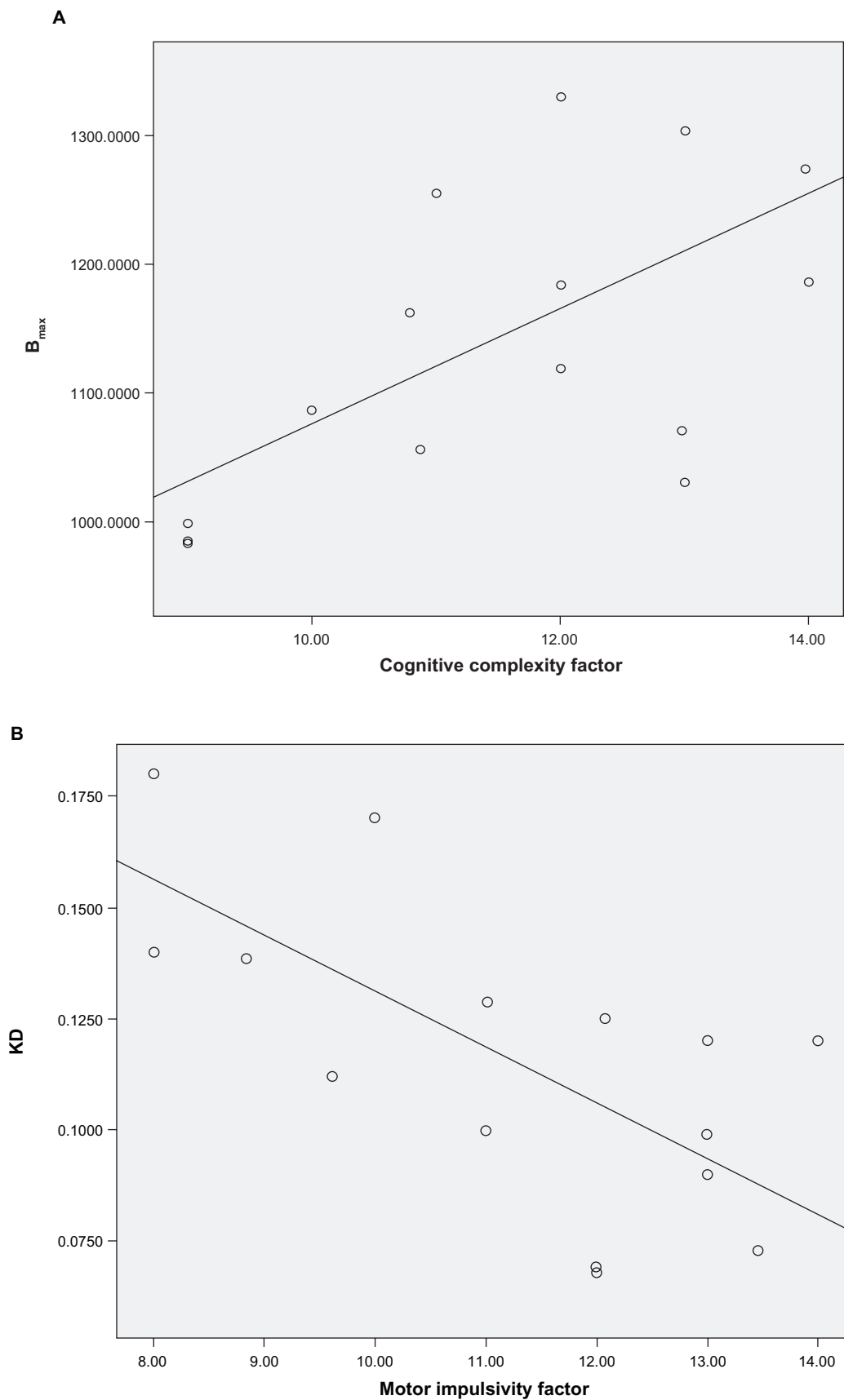
A

B

Figure 1 A) Positive correlation between the B_{max} and the cognitive complexity factor in men (Pearson correlation = 0.378, P = 0.006). **B**) Negative correlation between the Kd and the motor impulsivity factor in men (Pearson correlation = −0.673, P = 0.023).

$(t = -3.004, P = 0.006)$ and cognitive complexity $(t = -2.096, P = 0.046)$.

The correlation analysis showed that the B_{max} was significantly and positively related to the cognitive complexity factor of the whole sample (Pearson correlation = 0.378, $P = 0.047$), however, when distinguishing between the two sexes, it emerged that it was present only in men (Pearson correlation = 0.628, $P = 0.039$), while it was lacking in women (Figure 1a). Men showed also a significant and negative correlation between the Kd and the motor impulsivity factor (Pearson correlation = -0.673, $P = 0.023$) (Figure 1b).

Discussion

The present study explored and compared the possible differences in impulsivity characteristics, assessed by the BIS-11 questionnaire, in a group of healthy volunteers of both sexes, as well as the eventual correlations with the platelet SERT, evaluated by means of the ^{3}H-Par binding parameters (the maximum binding capacity, B_{max}, and the dissociation constant, Kd). Although the ensuing findings are affected by some limitations which should be acknowledged, such as the small sample size, the evidence that all subjects belonged to the same setting and had similar life-habits, and that impulsivity was assessed by a self-report scale only, factors that perhaps limit their generalizability, nevertheless they are intriguing. It should be noted, however, that rarely, both self-report and behavioral measures have been used together.[54–56]

First, the women of our sample showed a higher BIS-11 total score than men, and even the scores of two BIS-11 factors, the so-called "motor impulsivity" and "cognitive complexity", were higher in women than in men. These findings would indicate that women are generally more impulsive than men, at least when considering impulsivity as a trait, construct at the basis of the BIS questionnaire. Most of the literature data are in disagreement with our observations, as men and women do not appear to be consistently different on impulsivity,[39,56,57] or men had higher scores at the BIS-11 questionnaire.[58] In addition, gender has been shown to modulate the link between impulsivity and some health-risk behaviors, such as nicotine use in women,[59,60] or alcohol intake in both men and women.[58,59,61,62]

Second, the correlation analysis revealed that the B_{max} of ^{3}H-Par binding, which is a measure of the number of the SERT proteins, was significantly and positively related to the BIS-11 cognitive complexity factor, but only in men. This means that the higher the density of the SERT proteins, the higher the score of the BIS-11 factor. The men of our sample showed also another significant, albeit negative, cor-

relation between the motor impulsivity factor and the Kd, which is the inverse of the affinity constant, that is to say, when the Kd is low, the motor impulsivity increases, and viceversa. These findings are consistent with the results of a previous study reporting that increased platelet SERT affinity (low Kd) correlated with higher ratings of aggressive and externalising beahvior in childhood attention deficit/hyperactivity disorder.[63] In addition, they can be considered in agreement with the general observations of disturbances of the serotonergic system, as shown blunted prolactin response to fenfluramine amongst male, but not female subjects with borderline personality disorder,[29,34,64–67] or lower prolactin or cortisol responses in healthy men,[36–38,68,69] or increased platelet 5-HT content in impulsive adolescents.[70] Moreover, in impulsive men the blunted prolactin response has been related to the short variant of the SERT promoter,[46] while in impulsive girls such a variant seems to predispose to higher sensitivity to environmental adversity.[71] Taken together, these findings suggest that 5-HT is more implicated in impulsivity in men than in women. Interestingly, it has been reported that acute tryptophan depletion increases impulsive response style in men only, without affecting mood.[72,73] Therefore, it seems that gender is an important factor in the modulation of 5-HT upon impulsivity.

In conclusion, the findings of the present study would suggest that impulsivity is a complex phenomenon, with multiple facets, and resulting from the interplay of different factors, in particular the 5-HT system, whose role on this behavior is strongly modulated by gender, although with no doubt other neurotransmitters are involved.[13]

Future studies should confirm or not our observations in larger sample of healthy subjects, as well as in patients with different impulse control disorders.

Disclosures

The authors report no conflicts of interest in this work.

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