

BRIEF COMMUNICATION

Alteration of the platelet serotonin transporter in romantic love

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ABSTRACT

Background. The evolutionary consequences of love are so important that there must be some long-established biological process regulating it. Recent findings suggest that the serotonin (5-HT) transporter might be linked to both neuroticism and sexual behaviour as well as to obsessive–compulsive disorder (OCD). The similarities between an overvalued idea, such as that typical of subjects in the early phase of a love relationship, and obsession, prompted us to explore the possibility that the two conditions might share alterations at the level of the 5-HT transporter.

Methods. Twenty subjects who had recently (within the previous 6 months) fallen in love, 20 unmedicated OCD patients and 20 normal controls, were included in the study. The 5-HT transporter was evaluated with the specific binding of ³H-paroxetine (³H-Par) to platelet membranes.

Results. The results showed that the density of ³H-Par binding sites was significantly lower in subjects who had recently fallen in love and in OCD patients than in controls.

Discussion. The main finding of the present study is that subjects who were in the early romantic phase of a love relationship were not different from OCD patients in terms of the density of the platelet 5-HT transporter, which proved to be significantly lower than in the normal controls. This would suggest common neurochemical changes involving the 5-HT system, linked to psychological dimensions shared by the two conditions, perhaps at an ideational level.

INTRODUCTION

Since falling in love is a natural phenomenon with obvious implications for the process of evolution, it is reasonable to hypothesize that it must be mediated by a well-established biological process. In this report we examine the relationship between the serotonin (5-HT) transporter, the state of being in love and obsessive–compulsive processes.

Recent investigations regarding the molecular mechanisms of sexual behaviour would suggest a hypothetical link between both the dopamine system and the serotonin (5-HT) transporter and conjugal and sexual behaviours (Hamer & Copeland, 1994; Lesch *et al.* 1996). The dopa-

mine system, which seems to underlie sexual behaviour with multiple partners, might in turn be mediated by high sensation- or novelty-seeking personality traits (Cloninger, 1986). This is best represented by cyclothymia with its alternating periods of intensity of emotional reactivity – both positive and negative – which might facilitate falling in and out of love with great rapidity and frequency (Akiskal *et al.* 1977, 1979); such a behaviour, however, is expected to be of short duration, because of the short length of hypomanic periods in cyclothymia. On the other hand, the 5-HT transporter, putatively linked to both neuroticism and sexual behaviour (Lesch *et al.* 1996), might mediate more enduring and ‘romantic’ forms of love, characterized by ‘obsessive’ pre-occupations about the partner and, consequently, a greater likelihood of bonding and faithfulness to the relationship.

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The role of 5-HT in obsessive-compulsive disorder (OCD) is supported by different findings, mainly by the consistent response of patients to 5-HT re-uptake inhibitors (Zohar & Insel, 1987; Montgomery, 1994; Greist *et al.* 1995; Piccinelli, 1995; Finiberg, 1996). Evidence of alterations in the serotonergic system in OCD is provided by challenge tests, with more or less specific serotonergic agonists and/or antagonists (Insel *et al.* 1985; Hollander *et al.* 1988), by cerebrospinal fluid measurement of 5-hydroxy-indoleacetic acid, the major 5-HT metabolite (Åsberg *et al.* 1981), as well as by the evaluation of the sodium and temperature-dependent 5-HT transporter in blood platelets, which shows striking similarities to that present in the central nervous system (Briley *et al.* 1979; Rausch *et al.* 1995). The transporter has generally been labelled by tritiated imipramine ($^3\text{H-IMI}$), a tricyclic antidepressant (Ieni *et al.* 1985; Marcusson *et al.* 1985; Meyerson *et al.* 1987; Hrdina, 1989). Insel *et al.* (1985) found no difference in both the 5-HT reuptake and the $^3\text{H-IMI}$ binding between healthy controls and OCD patients, and Weizman *et al.* (1986) and Marazziti *et al.* (1992) observed normal 5-HT reuptake coupled with a reduced number of $^3\text{H-IMI}$ binding sites. Black *et al.* (1990) replicated Insel *et al.*'s data of no change in $^3\text{H-IMI}$ binding, except for a decrease in clomipramine-treated patients, while other studies have shown a decreased number of $^3\text{H-IMI}$ binding sites and a decreased affinity for 5-HT uptake (Bastani *et al.* 1991), as well as an increased velocity of 5-HT reuptake, with no change in $^3\text{H-IMI}$ binding (Vitiello *et al.* 1991). Subsequently, it has been demonstrated that the more selective ligand $^3\text{H-Par}$ binds to a single site, probably corresponding to the neuronal transporter (Mellerup *et al.* 1983; Marcusson *et al.* 1988; Mann & Hrdina, 1992) and we have recently shown a significant decrease in the number of $^3\text{H-Par}$ binding sites in a group of 18 OCD patients, as compared with healthy controls (Marazziti *et al.* 1996).

The similarities between an obsession and an overvalued idea, such as that typical of romantic love, suggest a possible sharing of common alterations at the level of the 5-HT transporter. We, therefore, evaluated the 5-HT transporter, by means of the specific binding of $^3\text{H-Par}$, in a group of subjects who were

experiencing the early phase of falling in love (romantic love), in OCD patients and in a 'normal' control group.

METHOD

Subjects

Twenty subjects (17 female and three male, mean age \pm s.d.: 24 ± 3) who had recently fallen in love, were recruited from medical students, by means of advertisement. They were selected according to the following criteria: (a) the love relationship had begun within the previous 6 months; (b) the couple had had no sexual intercourse and; (c) at least 4 h a day were spent thinking of the partner. Twenty patients (10 female and 10 male, mean age \pm s.d.: 29 ± 6) who met current DSM-IV (APA, 1994) criteria for OCD, with neither a past nor a current history of mood disorders, were studied also. None had ever taken psychotropic drugs, except for two who had received fluvoxamine (200 mg and 300 mg, respectively) 1 month before. The age (mean \pm s.d.) at the onset of OC symptoms was 18 ± 5 and the length (mean \pm s.d.) of the disorder was 10 ± 9 years. The severity of the OCD symptoms was evaluated by means of the Yale Brown Obsessive-Compulsive Scale (Y-BOCS) (Goodman *et al.* 1986): the total score (mean \pm s.d.) was 19 ± 3 . The depressive symptoms were rated by means of the Hamilton Rating Scale for Depression (HRSD) (Hamilton, 1960) and the total score (mean \pm s.d.) was 4 ± 3 .

The 'normal' control group consisted of 20 healthy drug-free subjects (10 female and 10 male, mean age \pm s.d.: 29 ± 2), with neither a family nor a personal history of any major psychiatric disorder (Table 1).

The 'in love' subjects and the 'normal' group were also evaluated with the Y-BOCS and the HRSD. All subjects were free of physical illness

Table 1. Characteristics of the subjects

	Age (years) Mean (s.d.)	Y-BOCS Mean (s.d.)	HRSD Mean (s.d.)
Subjects in love 17 F, 3 M	24 (3)	8 (4)	2 (1)
OCD patients 10 F, 10 M	29 (6)	19 (3)	4 (3)
Healthy controls 10 F, 10 M	29 (2)	2 (1)	3 (1)

and gave their informed consent to be included in the study, which was approved by the Ethics Committee of the University of Pisa. Sixteen patients, out of the total of 20, were included in a previous study (Marazziti *et al.* 1996).

Procedure

Preparation of platelet membranes

Venous blood (20 ml) was collected between 8 and 9 a.m. and in the months March–June, to avoid the possible interference of circadian and seasonal rhythms, respectively, from fasting subjects and gently mixed with 1 ml of anti-coagulant 0.15 M EDTA. Platelet-rich plasma (PRP) was obtained by low-speed centrifugation ($200 \times g$, for 20 min, at 22 °C). Platelets were precipitated from PRP by centrifugation at $10\,000 \times g$ for 10 min at 4 °C, and washed with 8 ml buffer (150 mM NaCl, 20 mM EDTA, 50 mM Tris-HCl, pH 7.5, 4 °C). Pellets were lysed and homogenized in 8 ml buffer (5 mM Tris-HCl, 5 mM EDTA, pH 7.5, 4 °C) with an ultrathurrax homogenizer and centrifuged twice at $30\,000 \times g$ for 15 min at 4 °C. The ensuing pellet was then stored at -80 °C until the assay, which was performed within a week.

³H-Par binding

Platelet membranes were suspended in an assay buffer (50 mM Tris, 120 mM NaCl, 5 mM KCl, pH 7.4) and homogenized. The ³H-Par binding was carried out according to the method of Marazziti *et al.* (1996). The incubation mixture consisted of 100 μ l of platelet membranes (50–100 μ g protein/tube), 50 μ l of ³H-Par at six concentrations ranging from 0.01 to 1 nM, and 1850 μ l of assay buffer. Specific binding was obtained as the binding remaining in the presence

of 10 μ M fluoxetine (a gift from Eli-Lilly Co., Indianapolis, USA) as a displacer. All samples were assayed in duplicate and incubated at 22 °C for 1 h. The incubation was halted by the additions of 5 ml of cold assay buffer. The content of the tubes was immediately filtered under vacuum through glass fibre filters GF/C (Whatman) 2.5 cm in diameter and washed three times with 5 ml of assay buffer. Equilibrium-saturation binding data, the maximum binding capacity (B_{max} , fmol/mg) and the dissociation constant (K_d , nM) were analysed by means of the iterative curve fitting computer programs EBDA (McPherson, 1985).

Statistics

Statistical analysis was performed by means of the analysis of variance (ANOVA) for repeated measures followed by the *post hoc* procedure, according to Scheffé's method (Nie *et al.* 1975).

RESULTS

As shown in Table 2, the subjects who had recently fallen in love had a statistically significant lower density (B_{max} , fmol/mg protein, mean \pm s.d.) of ³H-Par binding sites than the controls (625 ± 219 v. 1324 ± 486 , $P < 0.001$), with no change in the K_d (nM, mean \pm s.d.) (0.24 ± 0.27 v. 0.17 ± 0.28), while they did not differ from patients with OCD (B_{max} , 736 ± 457 ; K_d , 0.16 ± 0.18).

No significant correlation between Y-BOCS or HRSD total scores and B_{max} or K_d values was observed.

When six of the 20 in-love subjects were retested for ³H-Par binding parameters 12 to 18 months later, the B_{max} and K_d values did not differ from those of healthy controls (B_{max} , 1214 ± 367 ; K_d , 0.21 ± 0.19).

DISCUSSION

In subjects who had recently fallen in love and were still at the early, romantic phase of the relationship with no sexual intercourse, the density of the platelet 5-HT transporter was found to be lower than in normal controls and similar to that observed in a group of patients with OCD. Some might consider sexual intercourse as a necessary component of love. We think not, Stendhal (1842), the French

Table 2. Mean (s.d.) values for ³H-Paroxetine binding parameters, B_{max} (fmol/mg protein) and K_d (nM) in subjects with a romantic love, OCD patients and healthy controls

	B_{max} Mean (s.d.)	K_d Mean (s.d.)
Subjects in love	625 (219)***	0.24 (0.27)
OCD patients	736 (457)***	0.16 (0.18)
Healthy controls	1324 (486)	0.17 (0.28)

ANOVA, followed by *post hoc* procedure: subjects in love = OCD patients < healthy controls.

*** $P < 0.001$.

writer considered love as unconsummated passion. This aspect we believe underlies the obsessive pre-occupation so characteristic of the early stage of love (which, in rare instances, might persist for a lifetime of abstract idealization that leads to poetry and music dedicated to the love object). As far as we are aware, this is the first report of changes in the 5-HT transporter during a physiological state; it would suggest that being in love literally induces a state which is not normal – as indeed suggested by a variety of colloquial expressions used throughout the ages in different countries, all of which refer generally to falling ‘insanely’ in love or to being ‘lovesick’. It is noteworthy that the values of ³H-paroxetine binding parameters observed in healthy subjects is consistent with literature data, so that the finding in subjects in love should be considered as a ‘true’ decrease.

Certainly, emotions and feelings are the result of brain mechanisms, although different factors, not all biologically rooted, may be involved. Both physiological and pathological conditions involve the same brain systems and neurotransmitters. This is particularly evident for the 5-HT system, which seems to play a pivotal role in the regulation of a variety of functions and behaviours, from normality to mental disorders, such as feeding, thermoregulation, sleep, pain, arousal, sex and reproductivity, biological and neuroendocrine rhythms, to addiction, impulsivity, anxiety, depression and OCD (Jacobs & Forman, 1995).

A relationship between the functionality of the 5-HT transporter and personality traits (Lesch *et al.* 1996) or aggressive features (Coccaro *et al.* 1996) has already been observed. The present data, showing the same values of ³H-Par binding sites in subjects in the early romantic phase of a relationship as in OCD patients, would suggest the presence of similar changes in the 5-HT transporter in the two conditions, coupled perhaps with parallel changes in psychological dimensions. The notion that an overvalued idea, such as that typical of a romantic relationship or of the early phase of falling in love, might be related to a physiological obsessive state or even to a sort of ‘micro-paranoia’ can in fact be found in published psychiatric literature (Netter, 1989; Forward & Craig, 1991; Griffin-Shelley, 1991). We would suggest that a degree of overlapping may occur

at an ideational level, involving the dimension ‘certainty/uncertainty’ as well as that of ‘insight’/‘no insight’ (Insel & Akiskal, 1986). We would envisage a continuum from OCD (uncertainty/insight) through the overvalued ideation typical of romantic lovers (certainty/insight) to delusional states (certainty/no insight).

In conclusion, the statistically significant decrease in the number of the transporter proteins for 5-HT in the platelets of subjects who were in love and in those of OCD patients would seem to suggest a certain similarity between the two conditions. Such a similarity is strongly supported by the observation that the changes in the 5-HT transporter appear to be transient and state-dependent. Patients with OCD who have recovered following specific treatment, show an increase in ³H-Par binding site density (Marazziti *et al.* 1997), in much the same way that six subjects who were in love when re-tested 12–18 months after they had first started the relationship and who had no obsessive ideation regarding the partner at this time, had by then, in this regard, become indistinguishable from the normal controls.

We believe, therefore, that further studies could usefully be set up in order to explore para-physiological conditions that might serve as models for studying complex disorders, as well as helping to clarify the involvement of different neurotransmitters in physiological functions and behaviours.

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