

Changes in dopamine D2-receptor binding are associated to symptom reduction after psychotherapy in social anxiety disorder

S Cervenka¹, E Hedman^{1,2}, Y Ikoma^{1,3}, D Radu Djurfeldt¹, C Rück¹, C Halldin¹ and N Lindfors¹

The dopamine system has been suggested to play a role in social anxiety disorder (SAD), partly based on molecular imaging studies showing reduced levels of striatal dopaminergic markers in patients compared with control subjects. However, the dopamine system has not been examined in frontal and limbic brain regions proposed to be central in the pathophysiology of SAD. In the present study, we hypothesized that extrastriatal dopamine D2-receptor (D2-R) levels measured using positron emission tomography (PET) would predict symptom reduction after cognitive behavior therapy (CBT). Nine SAD patients were examined using high-resolution PET and the high-affinity D2-R antagonist radioligand [¹¹C]FLB 457, before and after 15 weeks of CBT. Symptom levels were assessed using the anxiety subscale of Liebowitz Social Anxiety Scale (LSAS_{anx}). At posttreatment, there was a statistically significant reduction of social anxiety symptoms ($P < 0.005$). Using a repeated measures analysis of covariance, significant effects for time and time \times LSAS_{anx} change on D2-R-binding potential (BP_{ND}) were shown ($P < 0.05$). In a subsequent region-by-region analysis, negative correlations between change in D2-R BP_{ND} and LSAS_{anx} change were found for medial prefrontal cortex and hippocampus ($P < 0.05$). This is the first study to report a direct relationship between symptom change after psychological treatment and a marker of brain neurotransmission. Using an intra-individual comparison design, the study supports a role for the dopamine system in cortical and limbic brain regions in the pathophysiology of SAD.

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Introduction

The dopamine system is involved in social behavior, learning and emotional regulation, predicting a role in the pathophysiology of social anxiety disorder (SAD). Molecular imaging studies have provided preliminary support for this hypothesis, showing reduced levels of striatal dopaminergic markers both pre- and postsynaptically in patients compared with control subjects.^{1–3} However, negative results have also been reported.⁴ A possible explanation for this inconsistency may be that none of the studies performed thus far have examined the dopamine system in limbic or prefrontal brain regions, which have shown to be involved in SAD based on brain activation studies (for a review, see ref. 5). In part, this has been due to methodological limitations, as the first generation D2-receptor (D2-R) positron emission tomography (PET) radioligands such as [¹¹C]raclopride have insufficient affinity for measurements in low-density extrastriatal brain regions.

PET studies have shown a marked inter-individual variability in levels of dopaminergic markers in healthy control subjects.⁶ This constitutes a drawback in studies where patients and control subjects are compared, as large sample sizes are needed in order to detect small differences. Furthermore,

group differences in biomarker levels do not directly infer causal links to disease symptoms. An experimental design where the biological marker is observed as a function of change in disease state could be considered a more powerful strategy in these respects. In psychiatry, the development of effective forms of psychotherapy offers a unique opportunity to improve symptoms without directly interfering with brain biochemistry. For SAD, cognitive behavior therapy (CBT) leads to clinical improvement in up to 75% of patients.^{7,8}

Although several studies have investigated the effect of psychotherapy on brain activation as assessed using PET and functional magnetic resonance imaging (MRI), reports on changes in neurotransmission have been scarce. Increased binding to the serotonin transporter in the midbrain after 12 months of psychodynamic therapy was demonstrated in a subgroup of patients with depression. No change was shown in dopamine transporter levels.⁹ In a subsequent study using PET and [¹¹C]WAY-100635, 5HT_{1a}-receptor binding was shown to increase in patients with major depressive disorder after brief psychodynamic psychotherapy.¹⁰ However, in neither of these studies a relationship could be shown between change in biomarker levels and symptom improve-

¹Department of Clinical Neuroscience, Division of Psychiatry, Karolinska Institutet, Stockholm, Sweden; ²Department of Clinical Neuroscience, Osher Center for Integrative Medicine and Division of Psychology, Karolinska Institutet, Stockholm, Sweden and ³Molecular Imaging Center, National Institute of Radiological Sciences, Chiba, Japan

Correspondence: Dr S Cervenka, Department of Clinical Neuroscience, Division of Psychiatry, Karolinska Institutet, Karolinska University Hospital Solna, Building R5, 171 76 Stockholm, Sweden.

E-mail: simon.cervenka@ki.se

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ment. Finally, in a recent study in patients with depression, no effect of psychodynamic psychotherapy was shown on dopamine D2-R binding in the striatum.¹¹ To date, no studies have examined the effect of CBT on markers of brain neurotransmission. As CBT is an intensive treatment with emphasis on repeated exposure to feared stimuli in order to reduce anxiety levels (for example, see ref. 12), this form of psychotherapy could be a more promising venue for detecting neurobiological correlates to symptom change.

In the present study, the primary objective was to investigate the role of the dopamine system in SAD using an inter-individual comparison design, by examining the relationship between change in symptom levels after CBT and change in dopamine D2-R binding. We predicted that increased binding potential (BP_{ND}) would be associated specifically with reduced anxiety levels in social situations. The study was performed using the high-affinity D2-R antagonist radioligand [¹¹C]FLB 457,¹³ which enables measurements in extrastriatal brain regions of particular interest for SAD, and examinations were conducted on a high-resolution research tomograph PET system for increased anatomical precision.¹⁴

Materials and methods

Subjects. Nine patients with SAD were recruited from a study comparing CBT administered via the Internet versus group therapy, the results of which have been reported elsewhere.¹⁵ As part of the treatment study, all subjects were interviewed by a senior psychiatrist and were found to fulfill DSM IV criteria for SAD¹⁶ using the Structured Clinical Interview for DSM-IV axis I disorders. Comorbidity, including drug addiction and abuse, was assessed using the Mini-International Neuropsychiatric Interview.¹⁷ After inclusion in the PET study, patients were randomized to treatment either in group format or treatment via the Internet. Subjects were healthy as determined by a physical examination and routine blood tests as well as a brain MRI examination. Three subjects had previously been treated with serotonin or serotonin and noradrenaline reuptake inhibitors, but none had received pharmacological treatment for SAD during the 2 months preceding the study. None were nicotine users. One patient fulfilled criteria for concurrent panic disorder with agoraphobia, otherwise no comorbidity was present. For additional subject characteristics, see Table 1. The study was approved by the Regional Ethics Review Board as well as the Radiation Safety Committee at the Karolinska Hospital, Stockholm. Subjects were included only after giving informed consent in writing.

Symptom ratings. At inclusion in the treatment study and after treatment, patients were assessed with the clinician-administered Liebowitz Social Anxiety Scale (LSAS).¹⁸ A self-rating version of the same scale (LSAS-SR)¹⁹ was completed via the Internet directly before and after treatment. LSAS is composed of two subscales, one measuring anxiety in a range of different situations (LSAS_{anx}), and the other assessing the degree of avoidance in the same situations (LSAS_{avoid}). As we hypothesized that D2-R binding would be

Table 1 Patient demographics

Patient	Age (years)	Sex	Duration of disorder (years)	Family history	Pre LSAS score
1	23	F	7	–	41
2	38	M	31	+	71
3	23	M	15	–	63
4	58	F	45	–	72
5	37	F	31	+	84
6	30	F	19	+	43
7	26	F	3	–	41
8	35	F	28	–	76
9	25	M	10	+	44

Abbreviations: F, female; +, indicates at least one of parents affected; LSAS, Liebowitz Social Anxiety Scale; M, male.

related primarily to anxiety levels, LSAS_{anx} was the outcome variable of main interest. In several cases, the time between clinical rating and PET examinations was extended up to several months, and in some instances the rating was performed by different psychiatrists before and after treatment. Therefore, only LSAS-SR scores were included in the analysis. PET1 was performed on average 13 ± 14 (mean \pm s.d.) days before pre-treatment ratings, and the time between post-treatment ratings and PET 2 was 17 ± 15 days.

Treatment. Three patients received cognitive behavioral group therapy¹² and six patients Internet-based CBT.²⁰ The duration of treatment was 15 weeks in both conditions. The treatment employed in the study, in both delivery formats, followed a CBT-model stressing the importance of avoidance and safety behaviors as well as misinterpretations of social events and internal focus as maintaining factors of SAD.^{21,22} The theoretical basis and proposed mechanisms were the same and the main finding from the treatment study, from which the present sample was recruited, was that Internet-based CBT and group CBT yield equivalent treatment effects.¹⁵ The median number of completed sessions or modules for both delivery formats was 13 of 15 (mean = 11.5; s.d. = 3.5). All participants were exposed to the main components of the treatment.

MR examinations. As part of the inclusion process, all patients performed a T1- and T2-weighted MRI examination using a 1.5T GE Signa Scanner (Milwaukee, WI, USA). The T2 image was inspected for macroscopic pathology, and the T1 image was used for the subsequent image analysis.

Radiochemistry. The radioligand [¹¹C]FLB457 is a substituted benzamide with the affinity of 0.02 nmol l^{-1} for D2 and D3 dopamine receptors *in vitro*, which is significantly higher than that of [¹¹C]raclopride ($1\text{--}2 \text{ nmol l}^{-1}$).¹³ This characteristic allows for examination of extrastriatal brain regions where D2-R densities are low. [¹¹C]FLB457 was synthesized as described previously.²³ The injected dose for PET1 and PET2 was 468 ± 16 and $465 \pm 19 \text{ MBq}$, respectively. For technical reasons, information on specific activity and total mass injected was lost for one PET1 and one PET2, respectively. For the remaining examinations, the average

specific activity was 1436 ± 2348 and $658 \pm 583 \text{ GBq } \mu\text{mol}^{-1}$ for PET1 and PET2, and the mass of injected FLB 457 was 0.41 ± 0.3 and $0.58 \pm 0.6 \mu\text{g}$, respectively. The injected dose, specific activity and mass did not differ between pre- and posttreatment ($P > 0.5$, paired *t*-test), and importantly, there was no correlation between injected mass and either BP_{ND} or symptom change.

PET examinations. PET examinations were performed on a high-resolution research tomograph system (Siemens Molecular Imaging, Knoxville, TN, USA). Before the first PET examination, a plaster helmet was manufactured for each subject individually to reduce head movement during measurements. The time between PET1 and PET2 was 146 ± 23 days. Average time for injection was 12:24 for PET 1 and 11:53 for PET2. Before the emission, a 5-min transmission scan was performed to correct for attenuation and scatter. [^{11}C]FLB 457 was injected in the antecubital vein as a bolus dose and radioactivity was measured for 87 min. For two subjects, the second examination was interrupted between 910 and 1416 s and 3361 and 3623 s, respectively. These intervals were excluded from the subsequent kinetic analysis. Images were reconstructed using the ordinary Poisson three-dimensional ordered subset expectation maximization including the point spread function algorithm, yielding in an in-plane resolution of 1.5 mm at half-maximum at the center of field-of-view.¹⁴

Image analysis. PET images were corrected for head movement using a frame-by-frame realignment procedure,²⁴ with each frame of the image serving as a reference to the next.

T1 MR images were realigned to the anterior commissure – posterior commissure plane. Regions of interest (ROIs) were manually defined on the MRI for each subject individually, using Human Brain Atlas software²⁵ (Figure 1). Regions chosen were amygdala, hippocampus and prefrontal cortices, based on their proposed role in SAD,⁵ and ROIs were defined using previously published guidelines.^{26,27} The prefrontal cortex was divided into dorsolateral, medial and orbitofrontal regions.²⁷ Striatal regions were not evaluated, as the high affinity of [^{11}C]FLB 457 does not allow for equilibrium within the frame of a PET experiment, thus preventing meaningful calculations of radioligand binding.²⁸ MRIs were segmented into gray matter, white matter and cerebrospinal fluid, and coregistered to each of the two PET images using SPM5. The transformation parameters obtained were used to subsequently apply the ROIs on the dynamic PET images to generate time activity curves (TACs). For frontal cortical regions, only voxels belonging to the gray matter segment was included in the ROI. Also, partial volume effect correction using the Meltzer method was applied for these regions to avoid smearing effects from neighboring CSF voxels.²⁹ Image processing was performed on SPM5 operating on Matlab R2007b (MathWorks, Natick, MA, USA).

BP_{ND} was calculated from the TACs using the simplified reference tissue model (SRTM), with cerebellum as reference. In this context, BP_{ND} represents the ratio at equilibrium of specifically bound radioligand to that of nondisplaceable radioligand in tissue.³⁰ The SRTM has previously been validated for [^{11}C]FLB 457.²⁸ Since we had no hypothesis of side differences in the involvement of dopaminergic neurotransmission in SAD, BP_{ND} for all regions was calculated

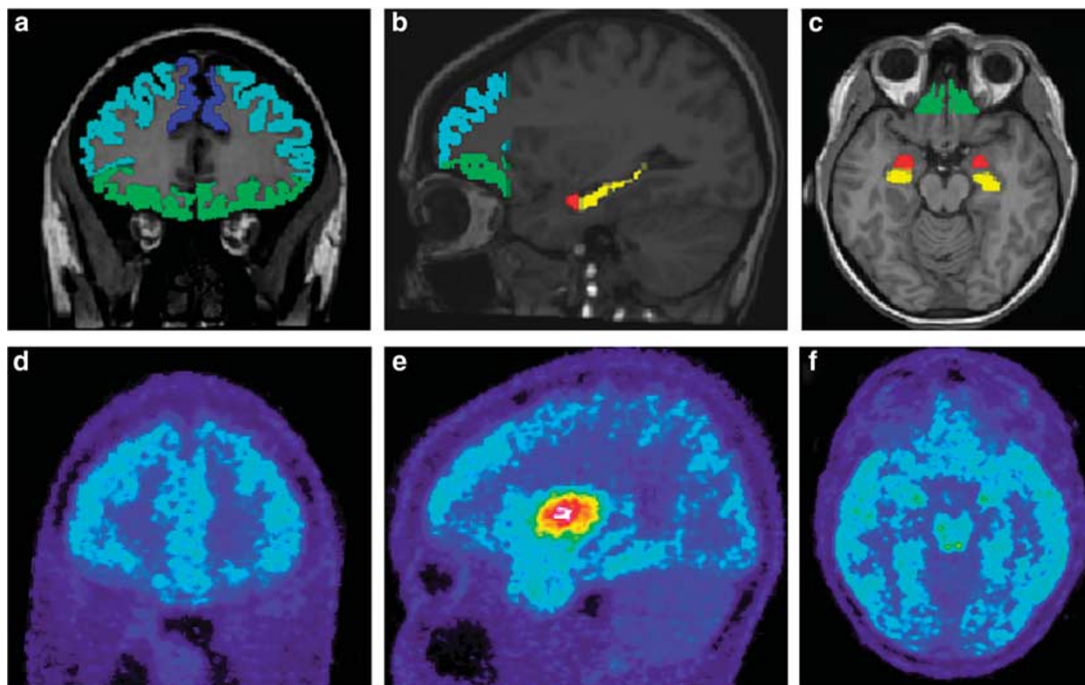


Figure 1 (a–c) Magnetic resonance images with regions of interests for amygdala (red), hippocampus (yellow), dorsolateral prefrontal cortex (cyan), medial prefrontal cortex (blue) and orbitofrontal cortex (green). (d–f) Summed images of [^{11}C]FLB 457 binding from the same patient, in corresponding coronal, sagittal and horizontal projections.

Table 2 D2-receptor-binding potential and symptom scores pre- and posttreatment

	Pre		Post		% Change		Paired t-test	
	m	s.d.	m	s.d.	m	s.d.	t	P
Dorsolateral PFC BP _{ND}	1.34	0.39	1.28	0.31	-3.6	8.7	1.45	0.186
Medial PFC BP _{ND}	1.17	0.30	1.13	0.27	-2.6	8.3	0.91	0.388
Orbitofrontal cortex BP _{ND}	1.43	0.38	1.39	0.33	-1.5	8.3	1.20	0.266
Amygdala BP _{ND}	3.51	0.49	3.55	0.51	2.3	16.6	-0.21	0.842
Hippocampus BP _{ND}	1.21	0.22	1.20	0.27	-0.4	15.9	0.18	0.861
LSAS total	59.4	17.2	31.7	11.2	-45.6	15.7	5.85	0.000
LSAS anxiety	32.3	9.5	19.3	6.7	-38.5	19.0	4.74	0.001
LSAS avoidance	27.1	8.2	12.3	5.3	-52.5	21.7	5.48	0.001

Abbreviations: BP, binding potential; LSAS, Liebowitz Social Anxiety Scale; m, mean; PFC, prefrontal cortex; s.d., standard deviation.

using spatially averaged TACs for right and left sides in order to improve TAC statistics.

Statistical analysis. Changes in LSAS scores and D2-R BP_{ND} were assessed using a paired *t*-test. Associations between D2-R BP_{ND} and LSAS scores at baseline were calculated using partial correlations, controlling for age. The relationship between changes in regional D2-R binding and changes in LSAS_{anx} scores was assessed using a repeated measures analysis of covariance, with time and region as within-subject factors and LSAS_{anx} percent change as a covariate. Secondary analyses were performed for LSAS_{avoid} and the two subscales combined. Subsequently, correlation coefficients were calculated between percent change in D2 BP_{ND} and percent change in LSAS_{anx} scores. In a *post-hoc* analysis, individuals were divided into responders ($\geq 50\%$ symptom reduction) and non-responders, and group differences in change in BP_{ND} values were explored using a one-way analysis of variance. For all tests, results were considered significant at $P < 0.05$. Statistical analysis was performed using PASW 18 (SPSS, Chicago, IL, USA).

Results

Changes in social anxiety levels and D2-R BP_{ND}. All patients improved after treatment, and the change in total LSAS scores as well as anxiety and avoidance subscales was statistically significant (Table 2). There was no difference in LSAS change between patients receiving group therapy and patients treated via the internet, either for the whole scale or for subscales ($P > 0.74$). At posttreatment, four (44%) participants no longer met diagnostic criteria for SAD. On a group level, the difference in D2-R-binding pre- and posttreatment did not reach statistical significance for any of the regions, as assessed using a paired *t*-test (Table 2). However, the direction and degree of change showed a considerable interindividual variability, which enabled computation of meaningful correlations with symptom change.

Associations between D2-R BP_{ND} change and social anxiety change. In the repeated measures analysis of covariance, significant effects for time and time \times symptom score change were shown for LSAS_{anx} ($F = 7.61$, $P = 0.028$ and $F = 7.77$, $P = 0.027$). In a subsequent region-by-region

analysis, negative correlations between change in D2-R BP_{ND} and LSAS_{anx} change were shown for dorsolateral prefrontal cortex ($r = -0.78$, $P = 0.013$), medial prefrontal cortex ($r = -0.82$, $P = 0.007$) as well as for hippocampus ($r = -0.81$, $P = 0.008$; Figure 2). The correlations in medial prefrontal cortex and hippocampus survived Bonferroni correction (adjusted P -value < 0.01). In these regions, responders showed an increase in binding (5.0% and 9.5%, respectively, $n = 4$), whereas non-responders on average showed a decrease (-8.6% and -8.3% , $n = 5$). Despite few individuals in each group, this difference was significant for MFC ($P = 0.003$) and trend-level significant for hippocampus ($P = 0.097$). There was no significant effect of time or time \times symptom change on the avoidance subscale. This difference of effects between subscales was also reflected in that when combining the two scales as covariate, trend-level effects were observed for time ($F = 3.93$, $P = 0.088$) and the interaction term for time \times change ($F = 3.74$, $P = 0.095$).

Pre- and posttreatment correlations between D2-R BP_{ND} and social anxiety. There was no correlation between D2-R BP_{ND} and LSAS_{anx} or LSAS_{avoid} scores pre- or posttreatment, after controlling for age.

Discussion

In this study, we assessed the role of the extrastriatal dopamine system in SAD, by examining changes in dopamine D2-R binding as a function of symptom change after CBT. Importantly, the aim of this study was not to examine the effects of psychological treatment on D2-R binding in SAD, as this would entail the use of a control condition. Instead, CBT was used as a tool to alter the disease state non-pharmacologically. Consequently, the association between change in symptom scores and changes in receptor binding was the primary outcome, rather than changes pre- and posttreatment on a group level. Accordingly, whereas the average difference between PET1 and PET2 was within the test-retest variability shown previously for [¹¹C]FLB 457,³¹ the interindividual variability in change was sufficient for correlative analyses. Using a similar design, changes in D1-receptor binding was recently shown to be related to improvement in working memory capacity after working memory training,³² and we now the first time demonstrate a direct relationship between symptom reduction after

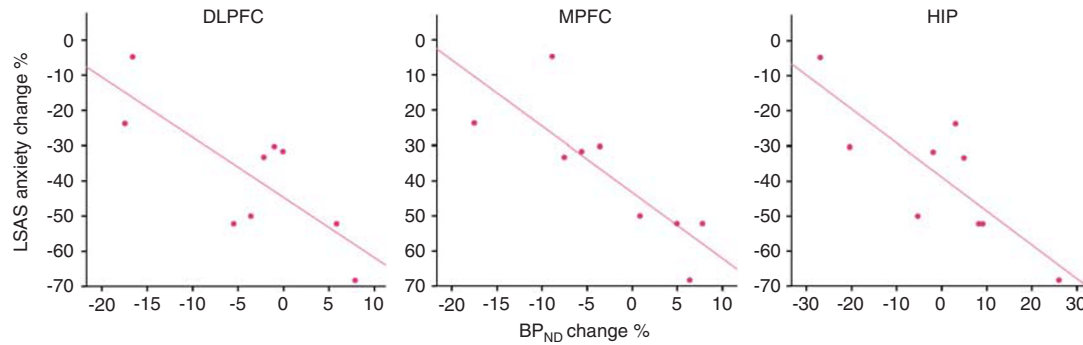


Figure 2 Scatterplots indicating relationships between change in Liebowitz Social Anxiety Scale (LSAS) anxiety scores and dopamine D2-receptor-binding potential (BP) in dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (MFC) and hippocampus (HIP).

psychotherapy and change in a marker of brain neurotransmission.

A role for the dopamine system in social behavior has been demonstrated in both animal research and human studies. Molecular imaging studies have shown negative correlations between striatal DA markers and the personality trait detachment as well as different measures of social conformity and low social status.^{33–39} Recently, we extended this line of research by demonstrating a relationship between social desirability and D2-R binding in the medial temporal lobe as measured using [¹¹C]FLB 457.⁴⁰ In the interpersonal domain, these personality traits can be viewed to indicate social submission as opposed to social dominance,⁴⁰ and the results thus mirror research on rodents and non-human primates where dopaminergic neurotransmission has been linked to the dimension of dominance-submissive behavior.^{41–44} Of particular interest is the study by Morgan *et al.*,⁴⁴ where D2-R binding in monkeys was shown to change as a function of hierarchical rank as the animals moved from individual to social housing. The observation of a relationship between change in D2-R binding and social anxiety symptoms is congruent with these lines of research and can be viewed as support for a suggested link between the dominant-submissive dimension of interpersonal behavior and SAD.⁴⁵ The correlation was not significant for LSAS_{avoid}, which may be explained by the more heterogeneous nature of avoidant behavior. For instance, reduced avoidance with maintained safety behaviors is not expected to yield less anxiety.²¹

SPECT studies have previously shown reduced dopamine D2-R binding in the striatum in 10 patients with SAD, as well as in a sample of 7 with comorbid OCD in comparison to control subjects.^{1,2} On the presynaptic side, lower dopamine transporter binding was demonstrated in 11 patients.³ In a more recent study using PET, no difference was shown in D2-R availability, either at baseline or after an amphetamine challenge, and there was also no difference in binding to the dopamine transporter ($n=15$, 12 and 12, respectively).⁴ However, none of these studies assessed dopamine receptors in extrastriatal brain regions.

In brain activation studies, one of the most replicated findings is increased activation in amygdala in response to fearful social stimuli^{46–48} but notably, negative findings have also been reported.^{49,50} Other regions showing altered activation in SAD include hippocampal and prefrontal cor-

tices.^{5,46,47,51–53} For the medial prefrontal cortex, a role specifically for monitoring social evaluation has been shown in SAD patients^{51,52} and this region is also implicated in fear extinction.^{54,55} Dopaminergic transmission in the hippocampus has shown to be involved in memory function in animal research as well as in molecular imaging studies.^{56–59} Taken together, the present findings of a correlation between dopaminergic function in hippocampus and prefrontal cortical regions may be related to the role of these regions in learning and social evaluation.

The primary limitation of this study is the small sample size. Although a total of 126 patients were included in the treatment study,¹⁵ for the present study we applied more strict inclusion criteria in order to avoid confounding effects on D2-R availability, for instance by the use of concomitant pharmacological treatment or nicotine. Furthermore, some patients were lost due to time constraints. Second, we cannot determine whether the changes in BP_{ND} are due to changes in receptor density or apparent affinity, as these parameters cannot be dissociated based on a single PET measurement.³⁰ Among the factors influencing apparent affinity, endogenous dopamine levels have shown to affect [¹¹C]FLB 457 binding,^{60–62} however, other studies have been negative.^{63,64} In rodents, where neurotransmitter levels are more accessible, increased DA release has been observed in response to stressful stimuli.^{65,66} Although studies employing multiple PET examinations with different specific activity of [¹¹C]FLB 457 have shown that receptor density accounts for most of the variance in BP_{ND},⁶⁷ it cannot be excluded that differences in endogenous dopamine levels could partly account for the associations observed, for instance reflecting higher DA reactivity during the examination procedure in patients with lesser improvement after treatment.

In conclusion, the results from this preliminary study indicate that plastic changes in the dopamine system may underlie reduced anxiety symptoms in SAD patients after treatment with CBT. The study supports a role for the dopamine system in SAD, and shows that intra-individual comparisons can be a promising approach in identifying brain biomarkers for psychiatric disorders.

Conflict of interest

The authors declare no conflict of interest.

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