

Increased Serotonin and Dopamine Transporter Binding in Psychotropic Medication–Naïve Patients with Generalized Social Anxiety Disorder Shown by ^{123}I - β -(4-Iodophenyl)-Tropane SPECT

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There is circumstantial evidence for the involvement of serotonergic and dopaminergic systems in the pathophysiology of social anxiety disorder. In the present study, using SPECT imaging we examined the ^{123}I - β -(4-iodophenyl)-tropane binding potential for the serotonin and dopamine transporters in patients with a generalized social anxiety disorder and in age- and sex-matched healthy controls. **Methods:** Twelve psychotropic medication-naïve patients with social anxiety disorder, generalized type (5 women and 7 men) and 12 sex- and age-matched healthy controls were studied. Volumes of interest were constructed on MRI-coregistered SPECT scans. Binding ratios were compared using the Mann–Whitney *U* test. Possible correlations between binding patterns and symptomatology were assessed using the Spearman rank correlation coefficient. **Results:** Significantly higher binding potentials were found for the serotonin in the left and right thalamus of patients. Patients had also a significantly higher binding potential for the dopamine transporter in the striatum. **Conclusion:** The present study provided direct evidence for abnormalities in both the dopaminergic and the serotonergic systems in patients with generalized social anxiety disorder.

Key Words: social anxiety disorder; beta-CIT; SPECT; 5-HTT; dopamine

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Social anxiety disorder (also known as social phobia) is a disabling condition that afflicts a large part of the general population. It tends to run a chronic and unremitting course and often leads to the development of alcoholism and

depression. The essential feature of social anxiety disorder is the fear of being evaluated by others with the expectation that such an assessment will be negative and embarrassing. Social anxiety disorder has been subdivided into 2 subtypes. The first subtype, referred to in the DSM-IV (1) as generalized social phobia, involves fear of a broad array of social situations. The second subtype, referred to as discrete or specific social anxiety disorder, is usually confined to 1 or 2 performance situations, of which public speaking is the most common (2). Given the clinical importance of social anxiety disorder, the neurobiology of this condition has received little attention to date.

Treatment studies demonstrating that selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors are effective in social anxiety disorder hint that serotonergic and catecholaminergic pathways have a role, but these findings can be only a rough guide in determining the neurobiology. Challenge tests with fenfluramine and m-chlorophenylpiperazine have provided other circumstantial evidence for the role of serotonin (5-hydroxytryptamine, or 5-HT) in social anxiety disorder (3,4). An involvement of the dopaminergic system in social anxiety was suggested by findings that homovanillic acid levels in cerebrospinal fluid tended to be lower in panic disorder patients with comorbid social anxiety disorder than in those without (5). Moreover, the prevalence of social anxiety disorder is increased in patients in whom Parkinson's disease develops (6). More recently, 2 neuroimaging studies have provided direct evidence that dopamine systems may play a role in the neurobiology of social anxiety disorder. Using ^{123}I -labeled 2- β -carbomethoxy-3- β -(4-iodophenyl)-tropane (^{123}I - β -CIT) as a tracer and SPECT, Tiihonen et al. found that the density of the dopamine transporter (DAT) in the striatum was reduced in patients with generalized social anxiety disorder (7). Schneier et al., using ^{123}I -iodobenzamide SPECT, found a reduced dopamine D_2 binding potential in this psychiatric condition (8).

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Although neuroimaging studies potentially could also provide direct evidence for a role of serotonergic systems in social anxiety disorder, to our knowledge only 1 such study has been published to date (9). In this study, by Lanzenberger et al., 5-HT receptor 1A binding in several limbic and paralimbic areas was found to be reduced in patients with social anxiety disorder.

^{123}I - β -CIT SPECT can be used to visualize both DAT and 5-HT transporter (5-HTT) in the human brain after a single administration of the ligand. Binding of ^{123}I - β -CIT in the striatal region has been shown to reflect mainly binding to DAT; binding in the thalamus, midbrain, and pons reflects predominantly binding to 5-HTT (10,11). The binding to DAT and 5-HTT can be further differentiated by using the difference in time course of ^{123}I - β -CIT uptake in DAT- and 5-HTT-rich brain regions (10). In the present study, we used this approach to investigate DAT and 5-HTT binding potentials in right-handed psychotropic medication-naïve patients with generalized social anxiety disorder (according to DSM-IV criteria) and no comorbidity and in healthy controls matched pairwise by age, sex, and handedness. We expected the binding pattern of ^{123}I - β -CIT to reflect abnormalities at the level of both 5-HTT and DAT.

MATERIALS AND METHODS

Subjects

The study was approved by the ethics committee of the University Medical Center, Utrecht, The Netherlands, and was performed in accordance with the ethical standards of the declaration of Helsinki. After a complete description of the study had been provided to the subjects, written informed consent was obtained. The patients came from direct physician referrals to our specialized anxiety clinic or reacted to advertisements. Healthy controls were enrolled through advertisements in flyers and newspapers or obtained from an existing database. Only subjects without a lifetime history of psychosis, substance abuse, recurrent major depression, bipolar disorder, eating disorders, other anxiety disorders, tics, and stuttering were included. All participants had no lifetime history of illnesses with possible central nervous system sequelae and were in good physical health, as confirmed by physical and laboratory examinations. Subjects consumed fewer than 6 cups of coffee and 3 units of alcohol a day and smoked fewer than 6 cigarettes a day. Screening for current and prior adult psychopathology was done by administering the Mini International Neuropsychiatric Interview Plus, version 5.0.0 (13). Diagnoses were confirmed by an experienced clinician. In addition, the Liebowitz Social Anxiety Scale (LSAS) was used to assess the severity of the social anxiety symptoms at entry (14). Handedness was determined by administering the Edinburgh Handedness Scale (15).

Subjects were excluded when they had a score of more than 13 on the 17-item Hamilton Depression Rating Scale (16). Subjects underwent imaging within 2 wk after inclusion. Any cognitive behavioral therapy had been terminated at least 3 mo before the study.

Twelve patients and 12 healthy controls were enrolled. All subjects completed the study. The patients and controls were perfectly matched for sex and did not differ significantly in age and handed-

TABLE 1
Demographic and Clinical Characteristics of Study Population

Characteristic	Patients (n = 12)	Controls (n = 12)
Mean age \pm SD (y)	39.4 \pm 12.6	33.0 \pm 9.5
Total Edinburgh Handedness Scale	0.95 \pm 0.04	0.96 \pm 0.03
Men (n)	7	7
Women (n)	5	5
Nonsmokers (n)	9	8
Length of illness (y)	23.9 \pm 14.7	
Total LSAS score	73.6 \pm 13.7	
Total Hamilton Depression Rating Scale	8.3 \pm 2.1	

Image Acquisition and Analysis

Images were acquired and analyzed using the same methods as in our previously reported study on patients with obsessive-compulsive disorder (17). On the first day of scanning, the subjects received an intravenous injection of approximately 150 MBq of ^{123}I - β -CIT (MAP Medical Technologies; radionuclidic purity [$^{125}\text{I}/^{123}\text{I}$] of at least 9.5×10^{-3} at calibration time and a radiochemical purity of at least 95%). We used a Prism 3000 triple-head γ -camera (Picker) with ultra-high-resolution fanbeam collimators and a full width at half maximum of approximately 12 mm. Four hours after the injection, the first scan was made to assess binding to 5-HTT. Between 22 and 24 h after the injection, the second scan was obtained to measure binding to DAT (18–20). The subjects refrained from coffee and nicotine in the 6–10 h preceding each SPECT scan. Immediately after the first scan, the subjects received 20 mg of paroxetine to displace the ^{123}I - β -CIT from 5-HTT so that binding to DAT could be determined more precisely (18). Several studies have demonstrated that at modest dosages (e.g., 10 mg) of paroxetine and other potent 5-HT reuptake blockers, occupation of 5-HTT is already virtually maximal (10,21,22). To control for possible differences in metabolism between subjects, we chose a higher oral dose of 20 mg. The 20-mg dose of paroxetine was well tolerated by all subjects. During scanning, subjects were supine, with eyes and ears open and head fixed in a head holder. We ensured that the patients stayed awake and did not move. For an accurate determination of each subject's volumes of interest (VOIs), all subjects also underwent structural MRI (3-dimensional fast field echo; echo time/repetition time, 4.6/30 ms; flip angle, 30°; field of view, 256 \times 256 mm; matrix, 128 \times 128 \times 130 mm; slice thickness, 2 mm) 2 h before the injection of ^{123}I - β -CIT. The MRI scans were reoriented to the standardized coordinate system of the Montreal standard brain (23). VOIs were delineated manually on the reoriented MRI scans by a researcher who was unaware of the subject's identity and diagnosis, by means of the display software from the Brain Imaging Center of the Montreal Neuroimaging Institute (24). Because the focus of our study was putative abnormalities at the level of 5-HTT in social anxiety disorder, the VOIs for 5-HTT included the left and right thalamus and the midbrain/pons region, whereas we limited the VOI for DAT to the left and right striatum taken together. Furthermore, this choice allowed a direct comparison of DAT findings with a previous study of Tiihonen et al. (7). We planned an exploratory post hoc analysis in which left and right striatal subregions would be delineated in cases in which the ROI striatum showed a significant

[Table 1] Demographic and clinical characteristics are shown in Table 1.

difference between patients and controls. The cerebellum was used as a reference region, representing nonspecific binding for ^{123}I - β -CIT.

To allow exact coregistration of MRI and SPECT scans, we used fiducial markers. Fiducial markers were cone-shaped, with cross-shaped feet, and were placed on the nose bridge and preauricularly above the mandibular joints. The position of each marker was indicated with 4 dots on the subject's skin to allow for repositioning of markers immediately before the SPECT scans. Vitamin A and ^{57}Co were used as contrast agents for the MRI and SPECT scans, respectively. The energy was set at a peak of 160 keV with a window of 20% for ^{123}I - β -CIT and at a peak of 120 keV with a window of 15% for ^{57}Co . After standard processing, brain SPECT images were resliced to isotropic voxels with dimensions of 2 mm and further treated as 3-dimensional volumes to coregister within the 3-dimensional orientation of the MRI scans. Coregistration was performed semiautomatically and was based on the position of the fiducial markers, using the Register multimodality software package and additional software developed at the Brain Imaging Center of the Montreal Neurologic Institute (25). The researcher performing the coregistration was unaware of subject identity and diagnosis.

For each separate VOI, the ratio of specific binding of ^{123}I - β -CIT to 5-HTT or DAT was calculated according to methodology used in previously published ^{123}I - β -CIT studies: the average radioactivity count per voxel per VOI minus the average radioactivity count per voxel in the cerebellum, divided by the average radioactivity count per voxel in the cerebellum.

Statistical Analysis

Age was compared using the Student *t* test. The interrater and intrarater reliability for VOI registration was assessed by calculating the intraclass correlation coefficients according to the method published by Bartko and Carpenter (26). The specific binding ratios for ^{123}I - β -CIT were compared using the Mann-Whitney *U* test. For 5-HTT binding, ratios in the midbrain/pons region and in the left and right thalamus were assessed; for DAT binding, the ratio in the striatum was assessed. Spearman rank correlation coefficients were calculated to assess correlations between specific binding ratios and LSAS scores. Two-tailed significance is reported throughout. Bonferroni correction for multiple comparisons (4 regions of interest) yielded an adjusted *P* value of less than 0.0125.

RESULTS

The intraclass correlation coefficients for the interrater and the intrarater reliability procedure for determining VOIs were between 0.86 and 0.99 (mean \pm SD, 0.95 ± 0.05) and 0.61 and 0.98 (mean, 0.81 ± 0.14), respectively. In 1 patient, only the 5-HTT uptake could be calculated; the last SPECT scan could not be reliably coregistered to the MRI scan because of motion artifacts.

The VOIs for the cerebellum were $104,208 \pm 16,211 \text{ mm}^3$ for patients and $93,943 \pm 11,445 \text{ mm}^3$ for controls. The VOIs for the midbrain/pons regions were $6,441 \pm 1,370 \text{ mm}^3$ for patients and $6,127 \pm 1,455 \text{ mm}^3$ for controls. The VOIs for the right thalamus were $3,962 \pm 855 \text{ mm}^3$ for patients and $4,544 \pm 1,678 \text{ mm}^3$ for controls, and the VOIs for the left thalamus were $4,051 \pm 914$ for patients and $4,610 \pm 686 \text{ mm}^3$ for controls. The VOIs for the right caudate were $3,142 \pm 519 \text{ mm}^3$ for patients and $2,933 \pm 608 \text{ mm}^3$ for controls, and the VOIs for the right putamen were $2,064 \pm 407 \text{ mm}^3$ for patients and $1,990 \pm 497 \text{ mm}^3$ for controls. The VOIs for the left caudate were $2,899 \pm 598 \text{ mm}^3$ for patients and $3,181 \pm 573 \text{ mm}^3$ for controls, and the VOIs for the left putamen were $2,022 \pm 478 \text{ mm}^3$ for patients and $2,064 \pm 407 \text{ mm}^3$ for controls. There were no significant differences in the sizes of the delineated VOIs between patients and controls.

There were no significant differences in normalized binding in the reference region between patients and controls; normalized cerebellar counts at 4 h were 20.38 ± 3.70 in controls and 20.90 ± 4.12 in patients, and at 22–24 h the counts were 3.75 ± 1.15 in controls and 3.37 ± 1.02 in patients.

The Mann-Whitney *U* test revealed that the average binding ratio for 5-HTT in the left and right thalamus was significantly higher in patients than in matched healthy controls ($P = 0.001$) (Fig. 1). No significant differences were found in the midbrain/pons region. The average binding ratio for DAT in the striatum was significantly higher in patients than in matched controls ($P = 0.011$) (Fig. 2). The

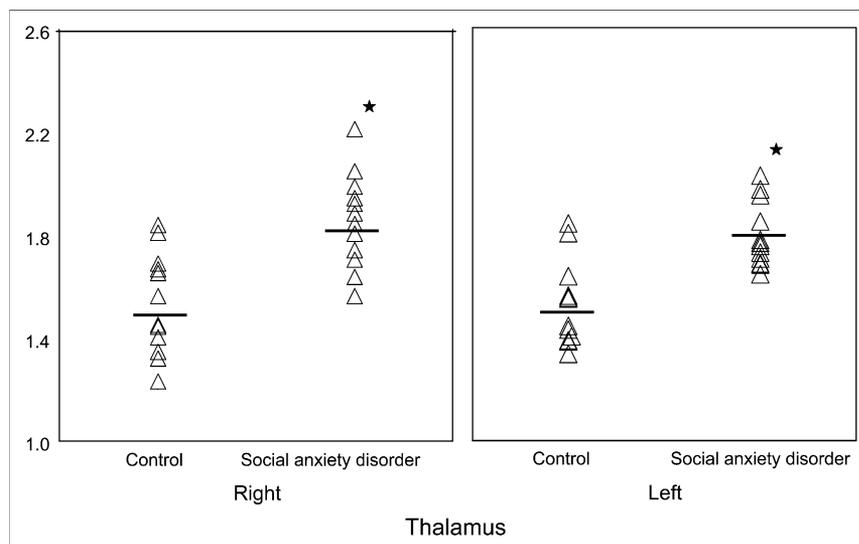


FIGURE 1. Binding ratios for 5-HTT in left and right thalamus of psychotropic medication-naïve patients with generalized social anxiety disorder ($n = 12$) and age- and sex-matched controls ($n = 12$) measured with ^{123}I - β -CIT SPECT. * $P = 0.001$; 2-tailed Mann-Whitney *U* test.

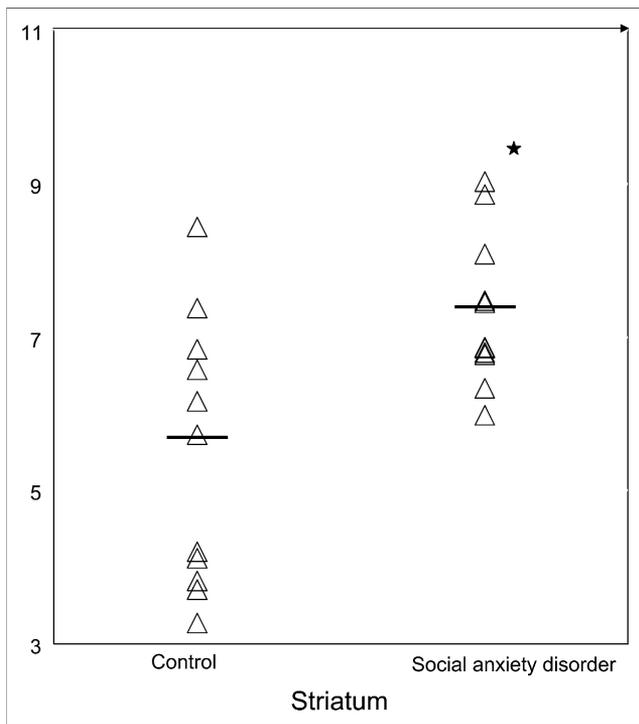


FIGURE 2. Binding ratios for DAT in striatum of psychotropic medication-naïve patients with generalized social anxiety disorder ($n = 12$) and age- and sex-matched controls ($n = 12$) measured with ^{123}I - β -CIT SPECT. * $P = 0.011$; 2-tailed Mann-Whitney U test.

binding ratios for 5-HTT and DAT in the regions of interest in patients and controls are summarized in Table 2. No significant correlations were found between LSAS score and DAT or 5-HTT binding potential in patients.

We performed an exploratory post hoc delineation and analysis for right and left striatum and for left and right putamen and caudate. This analysis revealed that DAT binding in the right putamen was significant higher in patients than in matched healthy controls, at a significance level uncorrected for multiple comparisons ($P = 0.012$).

TABLE 2
Average Binding Potentials for DAT and 5-HTT in Study Population

VOI	Patients ($n = 12$)	Controls ($n = 12$)	P (Mann-Whitney U test)
5-HTT			
Left thalamus	1.79 ± 0.12	1.52 ± 0.65	0.001*
Right thalamus	1.85 ± 0.19	1.53 ± 0.19	0.001*
Midbrain/pons	0.94 ± 0.10	0.90 ± 0.19	0.713
DAT			
Striatum	7.30 ± 0.98	5.47 ± 1.37	0.011*

*Value survived Bonferroni correction for multiple comparisons implying 4 regions of interest.
Data are mean \pm SD.

DISCUSSION

We found significantly higher ^{123}I - β -CIT binding ratios in the left and right thalamus (specific for 5-HTT) and in the striatum (specific for DAT) of psychotropic medication-naïve patients with generalized social anxiety disorder with no comorbid diagnosis, relative to the findings in healthy controls pairwise matched for age, sex, and handedness. No abnormalities in binding ratios in the 5-HTT-rich midbrain/pons region were found. No significant correlations were found between 5-HTT and DAT binding ratios and scores on the symptom rating scale (LSAS).

To our knowledge, this was the first study examining ^{123}I - β -CIT binding ratios both to 5-HTT-rich regions and to DAT-rich regions in patients with generalized social anxiety disorder. Our finding of an altered 5-HTT binding potential in the thalamus provides a direct indication that 5-HT has a role in the pathophysiology of generalized social anxiety disorder. Converging data have implicated a network of brain regions, including the prefrontal cortex, striatum, thalamus, and amygdala, in the pathophysiology of generalized social anxiety disorder (27,28). Most regions of this putatively involved network in social anxiety disorder are densely innervated by serotonergic or dopaminergic neurons. Impaired striatal-thalamic filtering of information relevant for social evaluation and an excessive conditionability of striatal-amygdala circuits may play a central role in the pathophysiology of social anxiety disorder (29).

Our finding of higher binding potentials of ^{123}I - β -CIT for 5-HTT in the thalamus of patients with social anxiety disorder can be interpreted as resulting from a decreased extracellular 5-HT concentration near the transporter (allowing ^{123}I - β -CIT to bind with higher density), from an elevated density of 5-HTT, or from a combination of both.

Decreased extracellular 5-HT levels in the brain of patients with social anxiety disorder would seem to be compatible with the fact that SSRIs are effective in social anxiety disorder (30). In line with this notion, it has been reported that repeated administration of SSRIs to healthy volunteers may increase social affiliation (31). More recently, Argyropoulos et al. showed that reducing 5-HT availability in the brain through tryptophan depletion resulted in a significant increase in challenge-related anxiety in successfully treated patients with social anxiety disorder (32). The hypothesis of a decreased serotonergic transmission remains in contrast to other reports suggesting that increased 5-HT neurotransmission is anxiogenic. Harmer et al. recently reported an impaired recognition of fearful facial expression in female volunteers after tryptophan depletion, whereas acute administration of the SSRI citalopram to healthy volunteers increased the recognition of fearful faces (33,34). Remarkably, SSRIs often display an acute anxiogenic effect that converts into anxiolysis on repeated administration. The mechanism responsible for this reversal is unknown but might be explained by adaptive changes (dampening) in the serotonergic system or in other more distal neuronal networks.

The heightened 5-HTT binding potential may also be the result of increased densities of 5-HTT in patients with social anxiety disorder, reflecting a higher homeostatic tone of the serotonergic system (with concomitant lower densities of 5-HT receptors). This possibility would be in line with results from Lanzenberger et al., who found reduced 5-HT receptor 1A levels in social anxiety disorder (9). Finally, the heightened 5-HTT binding potential may also be genetically determined. Arbelle et al. recently reported an association between the 5-HTT promoter region 44-base-pair insertion/deletion and shyness in a nonclinical sample of second-grade children (35). The investigators reported a significant association between the long 5-HTT promoter region 44-base-pair insertion/deletion polymorphism and shyness in their sample. Children who were homozygote for the long allele, which has been shown to produce higher gene transcription and presumably a higher density of 5-HTT, had significantly higher scores on the shyness scales (36). Insofar as shyness is an endophenotype for social anxiety disorder, the higher 5-HTT density may be interpreted as a risk factor for developing the disorder, which in turn may also explain our finding of a heightened 5-HTT binding potential. Unfortunately, the genetics of social anxiety disorder have not been adequately studied yet. Interestingly, a study by van Dyck et al. did not point at a direct association of higher central 5-HTT levels with the 5-HTT polymorphism but suggested a more complex relationship (37).

The higher DAT binding potential in the striatum observed in this study is at variance with data reported previously by Tiihonen et al., who found a decreased striatal dopamine binding potential in social anxiety disorder by using the same tracer (7). The difference in outcome between the 2 studies cannot be readily explained. The most obvious differences between the 2 studies are our more accurate assessment of the VOIs by using MRI scan coregistration and the inclusion of psychotropic medication-naïve patients without comorbidity in the present study. Both studies, however, had a small number of subjects—a limitation that always bears a risk of false-positive outcomes. As discussed above, when interpreting the data of our study, one must consider that the interaction between radiotracer and transporter is determined by the amount of radiotracer, the amount of transporter and its affinity, and the amount of competing ligands, that is, endogenous dopamine. Thus, the present finding can be interpreted as either a lower level of extracellular dopamine or an elevated density of DAT in patients with social anxiety disorder or a combination of both.

By and large, previous studies examining the dopaminergic system in social anxiety disorder seem to point to a decreased dopaminergic activity. Schneier et al. reported a lower ¹²³I-iodobenzamide binding potential for dopamine D₂ receptors in patients with social anxiety disorder. The authors attributed this finding to a lower dopamine activity (8). The lower binding potential, however, would also be reconcilable with either an enhanced dopaminergic activity or (transitory) high levels of dopamine near the receptors or an altered

affinity of the receptor, as was discussed by Mathew et al. (28). Heightened dopaminergic activity may decrease the density or affinity of D₂ receptors and simultaneously upregulate the density of DAT, whereas high levels of dopamine may compete with ¹²³I-iodobenzamide for receptor binding. Data from animal models have shown that a heightened dopaminergic activity in the striatum during stress can decrease D₂ receptor density (38). In line with the notion of an enhanced dopaminergic activity, Barnett et al. recently reported beneficial effects for the atypical antipsychotic olanzapine in patients with social anxiety disorder (39). Taken together, these findings suggest that our observation of a heightened density of DAT in the striatum is probably best explained by an elevated dopaminergic transmission. Interestingly, a recent functional MRI study using an implicit learning task as a probe of striatal functioning showed a reduced task-related activation of the striatum in patients with social anxiety disorder (40). Although several studies have implicated the striatum in seasonal affective disorder, the involvement of specific striatal subregions has been less thoroughly examined. With our exploratory post hoc analysis, we found increased DAT binding in the right putamen in seasonal affective disorder. However, this increase was significant at a level uncorrected for multiple comparisons, and the involvement of the putamen in seasonal affective disorder should be corroborated in other studies using other methodologies.

Clearly, the possible role of abnormalities in the dopaminergic and serotonergic systems needs to be further elucidated. Both dopamine (through D₁ and D₂ receptors) and 5-HT (through 5-HT receptor 2) are known to modulate the activity of excitatory (i.e., glutamate) and inhibitory (i.e., γ -aminobutyric acid) neurotransmitters in the striatum and related corticothalamolimbic circuitry. Data on the exact nature of these interactions are still inconclusive. Finally, based on the results of the present study, it is not possible to dissect out whether the found dopaminergic and serotonergic abnormalities are causal or epiphenomenal to social anxiety disorder. In our study, we found no significant correlations between scores on the clinical rating scale and abnormalities in the serotonergic and dopaminergic systems. In general, neuroimaging studies in psychiatry tend to find no or only weak correlations between the often heterogeneous symptomatology and neuroimaging measures. The previous ¹²³I- β -CIT study on social anxiety disorder also did not find correlations between binding ratios and symptomatology (7). The absence of any correlation in our and the previous study may be due to the psychometric properties of the used clinical scale and the heterogeneity of social anxiety disorder as defined by DSM-IV but can also be interpreted as pointing to the fact that the phenomena of social anxiety disorder are not directly related to the found abnormalities. It is also important to note the overlap between the binding patterns in patients and controls, suggesting that the found abnormalities may perhaps be more related to vulnerability or personality traits. Another explanation may be that the found

abnormalities are a consequence of having social anxiety disorder (i.e., a “scar” hypothesis).

Our study had several strong points. The patients and controls were pairwise-matched. The patients were psychotropic medication-naïve and had no comorbid diagnosis on axis I, and most had not received prior psychotherapy. Furthermore, the SPECT data were analyzed using coregistered MRI scans, allowing for more precise determination of VOIs. There were some potential limitations to the present study. The sample size was relatively small and we used a limited number of VOIs.

We visualized binding to 5-HTT only at 4 h after administration of the ligand. This time point for visualization, however, could have limited the possibility of finding further abnormalities at the level of 5-HTT, as was illustrated by the study of Willeit et al. on seasonal affective disorder (20). In that study, 5-HTT was visualized at 4 h after injection of ^{123}I - β -CIT and also at 24 h, when a pseudoequilibrium state is reached. Differences were found only in the SPECT acquisitions at 24 h after the injection. We followed the method described by Kuikka et al. and used paroxetine, 20 mg, to completely displace the ^{123}I - β -CIT from 5-HTT (18). Administration of paroxetine could potentially lead to an increase in symptoms of (social) anxiety, but such an increase (mild) was reported by only 1 patient.

Finally, although SPECT is easier to use, is less expensive, and has a higher safety index than PET, it also uses semi-quantitative techniques and has a poorer anatomic resolution.

CONCLUSION

Our data provide direct evidence for the involvement of both the dopaminergic and the serotonergic systems in the pathophysiology of social anxiety disorders. These findings need to be replicated and further explored in studies examining the effect of pharmacotherapy and psychotherapy on both the serotonergic and the dopaminergic transporter and receptor-binding capacities in generalized social anxiety disorder.

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