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Changes in midbrain serotonin transporter availability in atypically depressed subjects after one year of psychotherapy

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Abstract

Background: Psychotherapy is an effective treatment method for depression, but no differences in the psychotherapy response have been found between the subtypes of depression. The effect of psychotherapy on neurotransmitter transporter functions has never been recorded in depressed subjects.
Methods: Depressive outpatients ($N=19$) received psychodynamic psychotherapy for 12 months. All subjects fulfilled the DSM-IV criteria for depression, and 8 were classified as having atypical depression. The severity of depression was assessed with the 29-item Hamilton Depression Rating Scale (HAM-D-29). Midbrain serotonin transporter (SERT) and striatum dopamine transporter (DAT) densities were recorded using single photon emission computed tomography (SPECT) brain imaging with the [^{123}I]nor-β-CIT radioligand before and after psychotherapy.
Results: Midbrain SERT density significantly increased during psychotherapy in atypicals but not in nonatypicals. There were no changes in the levels of DAT.
Conclusions: The psychotherapy-related SERT elevation of atypically depressed subjects may be due to some unknown adaptive mechanisms inducing an increase in either the levels of SERT or serotonergic nerve terminals and therefore enhancing serotonergic activity and improving mood.

Keywords: Atypical depression; Depression; Dopamine transporter; Psychotherapy; Serotonin transporter; SPECT

1. Introduction

Alterations in serotonergic systems have been observed in major depressives, supporting the monoamine hypothesis of depression (Asberg et al., 1976; Quintana, 1992; Owens and Nemeroff, 1994). This depression-related monoamine loss has recently been associated with elevated monoamine oxidase A density (Meyer et al., 2006). Serotonin transporters (SERT) regulate serotonergic transmission through reuptake and removal of 5-HT from the synaptic cleft both in the brain and in peripheral serotonergic systems (Rudnick and Clark, 1993). Owens and Nemeroff (1994) proposed that SERT might play an essential role in the etiology of mood disorders. Decreased midbrain SERT

Abbreviations: ATD, atypical depression; ADDS, atypical depression diagnostic scale; β-CIT, [^{123}I]-2-β-carbometoxy-3-β-(4-iodophenyl)-tropane; ANCOVA, analysis of covariance; ANOVA, analysis of variance; CT, cognitive therapy; DAT, dopamine transporter; HAM-D, Hamilton depression rating scale; 5-HTTLPR, serotonin transporter-linked polymorphic region; IPT, interpersonal psychotherapy; MAOI, monoamine oxidase inhibitor; MAP*Psy Study, monoamine transporter function and autonomic regulation during psychodynamic psychotherapy study; MRI, magnetic resonance imaging; Nor-β-CIT, [^{123}I]-nor-2-β-carbometoxy-3-β-(4-iodophenyl)-tropane; NORT, noradrenergic transporter; ROI, region of interest; SD, standard deviation; SADS, schedule for affective disorders and schizophrenia; SERT, serotonin transporter; SPECT, single photon emission computed tomography; TG, therapy group.

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densities have been reported in depressed subjects compared with healthy controls in vivo (Malison et al., 1998; Joensuu et al., 2007), whereas Herold et al. (2006) observed no differences between depressed subjects and healthy controls in midbrain SERT availability when using a SERT-specific SPECT ligand [^{123}I]-ADAM. Furthermore, Meyer et al. (2004a) found no differences in SERT binding between major depressives and healthy controls in the prefrontal cortex, anterior cingulate, thalamus, bilateral caudate, or bilateral putamen in a [^{11}C]-DASB PET study.

The effectiveness of selective serotonin reuptake inhibitors (SSRIs) has been studied by assessing the proportion of blocked SERT binding sites in the brain. Meyer et al. (2004b) utilized highly selective [^{11}C]DASB PET to image SERT binding during SSRI treatment, and reported that the daily doses producing clinically significant differences over placebo were the same doses that produced an occupancy of 80% in the striatum. Furthermore, a higher pretreatment availability and greater occupancy of SERT in the diencephalon have been hypothesized to predict a better treatment response to SSRIs.

Alterations in SERT densities have also been reported in association with psychotherapeutic treatment. Three case studies, two with only one study subject (Saarinen et al., 2005; Viinamäki et al., 1998) and one with a study subject with mixed mania and six depressed controls (Tolmunen et al., 2004), have reported an increase in SERT densities in response to psychotherapy and recovery from major depression. Furthermore, Tolmunen et al. (2004) observed a decrease in the primarily elevated SERT level during psychotherapy in a patient with mixed mania. To our knowledge, no studies have been carried out with larger samples on changes in SERT or DAT densities in association with psychotherapy for major depression.

West and Dally (1959) reported that the monoamino-oxidase inhibitor (MAOI) iproniazid produced a better response in depressed patients with 'atypical patterns.' These patterns included 'phobic anxiety states with secondary depression' and the absence of many of the features of endogenous depression. The current DSM-IV criteria for atypical depression (ATD) were introduced in 1994. In DSM-IV, ATD is defined by the presence of mood reactivity and two or more of the following four features: hypersomnia, hyperphagia, leaden paralysis (a heavy, leaden feeling in the upper or lower limbs), and rejection sensitivity (American Psychiatric Association, 1994). ATD has been reported to have an earlier age of onset (Angst et al., 2002; Benazzi, 1999; Horwath et al., 1992; Stewart et al., 1993), and Angst et al. (2002) have reported higher rates of suicide attempts in atypically depressed subjects. Thus, ATD can be considered as an important subtype of major depression requiring scientific attention that focuses on improving the understanding of its biological basis and further facilitating the development of effective treatment methods. In a study by Mercier et al. (1992), 14 out of 25 atypically depressed subjects were reported to respond to cognitive therapy (CT). Jarrett et al. (1999) found CT and the MAOI phenelzine to be equally effective in subjects with ATD. CT has been suggested to reduce the relapse rate in patients with ATD (Jarrett et al., 2000). However, Stewart et al. (1998) found no differences in the response rate between subgroups of depression when CT and interpersonal therapy (IPT) were applied as treatment methods.

We have previously reported an absence of significant differences in SERT or DAT binding imaged with the [^{123}I]nor-β-CIT radioligand between melancholics and atypically depressed subjects (Lehto et al., 2006). However, there was an inverse correlation between atypical scores for the HAM-D-29 and the midbrain occupancy of [^{123}I]nor-β-CIT, suggesting a relationship between serotonergic dysfunction and ATD. In this study we sought to clarify the findings of our first cross-sectional study regarding the role of SERT in ATD. Based on previous findings reporting no difference in the clinical response to psychotherapy between atypicals and nonatypicals (Stewart et al., 1998), we hypothesized that both groups might respond similarly when measured with depression scales. However, we also assumed that a differential response might be observed in the change in neurotransmitter transporter levels of atypicals and nonatypicals.

2. Methods

2.1. Study design and subjects

This study on subjects with ATD formed part of an ongoing, larger investigation (Monoamine transporter function and autonomic regulation during psychodynamic psychotherapy; MAP*Psy) into the associations between psychodynamic psychotherapy and several biological variables, including SPECT imaging of neurotransmitter transporter densities, recording of heart rate variability and genotyping of study subjects, and with a follow-up designed to continue up to three years. The baseline examinations for this follow-up study were conducted during 2001–2005.

At baseline, severe or moderate depression (296.22, 296.23, 296.32, 296.33) was diagnosed in 29 outpatients referred to the rehabilitation and psychotherapy unit of the Department of Psychiatry, Kuopio University Hospital, Finland. The patients had not previously been administered psychotropic medication and had received no psychosocial treatment prior to entering the study. The subjects with psychotic disorders, bipolarity, substance abuse or severe personality disorders as well as somatic disorders were excluded from the study. Appropriate physical health and the absence of focal brain abnormalities were confirmed through clinical examination, laboratory testing and MRI imaging. The subjects who reported regular smoking were considered as smokers. After the baseline examinations, seven subjects fulfilling both the inclusion and exclusion criteria discontinued the study: five reported unwillingness in committing themselves to long-term psychotherapeutic treatment, one study subject discontinued due to a change of residence, and one subject decided seek help from a private psychotherapist.

The enrolled study subjects (N=22) were divided into two groups; one group of subjects (N=13) started therapy immediately after the clinical assessment (Therapy group 1; TG-1), and the other group (N=9) was assigned to a waiting-list for six months prior to psychotherapy (Therapy Group 2; TG-2). Patients were randomly assigned to either TG-1 or TG-2, and

the latter was designed to function as a waiting-list control group to assess the role of spontaneous recovery and compare the outcome of psychodynamic psychotherapy between these two groups of depressed subjects. The results from the comparison of the effects of psychotherapy intervention between these two groups are to be reported in full elsewhere. At Kuopio University Hospital, six months is the average duration of waiting before admission to psychotherapy, and we therefore considered the waiting-list control setting ethical. In this study we focused on the differences in SERT and DAT densities between the subtype of DSM-IV major depression showing atypical features and subjects with nonatypical depression after 12 months of psychodynamic psychotherapy.

Of the patients enrolled in this study, ten fulfilled the diagnostic criteria for ATD. Eight atypicals and five nonatypicals started therapy in TG-1 immediately after clinical assessment; two atypicals and seven nonatypicals were assigned to TG-2. In the final analysis, the study group comprised 19 subjects, as we excluded the TG-2 participants ($N=3$; two atypicals, one nonatypical) without clinically significant depressive symptoms according to HAM-D-17, i.e. those who scored seven or less (Hamilton, 2000) after being on the waiting-list for six months. The baseline measures were recorded before psychotherapy and the follow-up results were recorded after 12 months of psychotherapy. TG-1 and TG-2 were combined for the final analysis, in which we had 8 atypicals and 11 nonatypicals.

Due to the uneven distribution of atypicals and nonatypicals in TG-1 (8 atypicals, 5 nonatypicals) and in TG-2 (6 nonatypicals), we sought to estimate the effects of subtype or having been assigned to the waiting-list (i.e. belonging to TG-2). There was no difference in mean midbrain SERT levels between the TG-1 and TG-2 participants at the time of starting the therapy (TG-1: 1.13, SD 0.13; TG-2: 1.24, SD 0.14; $t=-1.57$, $p=0.14$).

Approval for the study design was obtained from the ethics committee of Kuopio University Hospital and was in accordance with the Declaration of Helsinki (World Medical Association 2004). All participants provided written informed consent after a full explanation of the study.

2.2. Psychiatric evaluation

Psychiatric diagnoses were based on clinical assessment and verified for all study subjects by a trained independent psychiatrist using the Structured Clinical Interview for DSM-IV-R (SCID-I; American Psychiatric Association, 1994). The atypical subtype was diagnosed using the atypical depression diagnostic scale (ADDS) (Stewart et al., 1993), which covers the DSM-IV criteria for atypical depression in a more comprehensive manner.

The severity of depression was assessed with the 29-item Hamilton Depression Rating Scale (HAM-D-29; Hamilton, 1960; Williams et al., 1988). The HAM-D-29 consists of the 21-item Hamilton Depression Rating Scale (HAM-D-21) with a supplementary 8-item addendum for scoring atypical depressive symptoms. The addendum includes questions concerning weight gain, increase in appetite, increased eating, carbohydrate craving, hypersomnia, leaden paralysis, and social withdrawal. The atypical index was calculated by dividing the atypical scores by the total scores for the HAM-D-29. The remission was defined as reduction of more than 50% in the HAM score between baseline and follow-up (Fava and Davidson, 1996).

2.3. Psychotherapy

Therapy lasted for one year for all participants. All psychotherapists had formal post-graduate training in psychodynamic psychotherapy. The focus of the psychotherapy was set on the depression-related psychodynamic processes and their manifestations, and the development of life-management skills along with the therapy process. The therapy sessions were scheduled twice a week, and the duration of one session was 45 min. The total number of therapy sessions was approximately 80.

2.4. Imaging procedure

SPECT imaging was performed on the female subjects on the Wednesday following menstrual bleeding that preceded the psychotherapy and on 12-month follow-up. A dose of 185 MBq of [^{123}I] nor-β-CIT (supplied by MAP Medical Technologies OY, Tikkakoski, Finland) was diluted in a volume of 10 ml physiological saline. The specific activity was higher than 1.8×10^{11} Bq/μmol (Hiltunen et al., 1998). The dose was slowly injected into the right antecubital vein in a dimly lit and quiet room. The scan-duration was 25 min. Serial SPECT scans (5 min, 6 h and 24 h) were performed on a dedicated Siemens MultiSPECT 3 gamma camera with fan-beam collimators (Siemens Medical Systems; Hoffman Estates I11., USA) (Kuikka et al., 1993). The whole time–activity curve was used in analysis using the reference tissue model of Acton et al. (1990). Head positioning was monitored during acquisition by using two position lasers.

2.5. Data analysis

The SPECT scans were decay-corrected and reconstructed with Butterworth-filtered back-projection in a 128×128 matrix with a pixel size of 3×3 mm, and were attenuation-corrected with Chang's algorithm (Hiltunen et al., 1998; Kuikka et al., 1993). The imaging resolution was 8–9 mm. The SPECT slices were consecutively summarized to the slice thickness of 6 mm and re-aligned using a Siemens semi-automatic brain quantification program and the Talairach coordinates (Talairach and Tournoux, 1993). The slices were rotated and re-aligned so that transaxial (x-direction), sagittal (y-direction) and coronal (z-direction) ones were at right angles to each other.

Region of interest (ROI) placement was based on a Siemens semi-automatic brain quantification program. The nuclear medicine specialist who performed the ROI analysis was unaware of whether the subjects were patients or controls. No true partial volume corrections were performed due to methodological difficulties. However, to avoid scatter and overlapping of the neighborhood compartments (such as the substantia nigra in the case of the raphe) the lower threshold of 60% of the maximum count was used to reduce the volume

averaging and partial volume errors. The ROIs were the striatum rich in DATs, and the midbrain rich in SERTs. They were manually drawn with the help of MRI data. The manual coregistration was confirmed visually. The cerebellum served as a reference region because the densities of SERTs and DATs are known to be extremely low in this area (Backstrom et al., 1989). It was assumed that the cerebellum corresponds to a two-compartment model (unbound tracer in arterial blood and free plus non-specifically bound tracer in the tissue) (Acton et al., 1990). The specific binding density in ml/ml for SERT and DAT was calculated using the noninvasive Logan method (Logan et al., 1996). The slope of this plot is equal to distribution volume ratio: (Region − Cerebellum) / Cerebellum = BP_{ND} − 1. The striatal uptake was pooled.

Magnetic resonance imaging (MRI) of the brain was performed within two weeks of the SPECT imaging to exclude structural pathology and to provide a high-resolution three-dimensional neuroanatomic background for the SPECT findings. The MRI findings were within the normal range in all subjects.

2.6. Reproducibility of SPECT

Reproducibility of the SPECT scan had previously been studied with eleven healthy subjects (5 males and 6 females; age range 20–39 y). SPECT studies were performed twice with a 12-month interval. The correspondence between the studies was good, with the mean difference (±standard deviation, SD) being 0.00±0.08 for SERT (mean and SD: 1.27±0.11 and 1.27±0.14, respectively) and 0.04±0.18 for DAT (mean and SD: 2.49±0.28 and 2.45±0.27, respectively). The intraclass correlation coefficient was 0.82 ($p<0.01$) for SERT and 0.79 ($p<0.01$) for DAT (unpublished data).

2.7. Statistics

The Student's *t*-test, Mann–Whitney *U*-test and Fisher's exact test were used to assess differences between the groups, and the paired samples *t*-test and Wilcoxon signed-rank test to assess the change in the depression scales and in transmitter densities during psychotherapy. Parametric tests were used when the distributions of the variables were normal and non-parametric tests were used when distribution of the variables was skewed. Pearson's correlation coefficient was used to assess the correlation between the changes in neurotransmitter levels and the change in the depression scales. To assess the differences in the changes of SERT and DAT densities between the groups, analysis of variance (ANOVA) was used in univariate analysis and analysis of covariance (ANCOVA) in multivariate analysis. A *p*-value of less than 0.05 was considered to indicate statistical significance.

3. Results

The groups of atypical and nonatypical subjects differed at baseline in atypical scores and in the atypical index. However, after 12 months of psychotherapy there were no differences between the groups in any measures (Table 1, Figs 1 and 2).

Table 1
Characteristics of the study groups at baseline and after 12 months of psychodynamic psychotherapy

	Baseline	*p* for difference between groups	12 months	*p* for difference between groups	*p* value for the change during the follow-up
Age, y					
Atypicals	28.2 (7.3)	0.75 [a]			
Nonatypicals	27.1 (7.3)				
Female gender, *n* (%)					
Atypicals	6 (75)	0.16 [b]			
Nonatypicals	11 (100)				
Smoking, *n* (%)					
Atypicals	3 (38)	1.00 [b]			
Nonatypicals	3 (27)				
Remitted subjects (%)					
Atypicals	3 (38)	1,00 [b]			
Nonatypicals	5 (46)				
HAM-D-21 scores					
Atypicals	19.13 (3.94)	0.31 [a]	12.50 (6.82)	0.57 [a]	0.02 [c]
Nonatypicals	22.18 (7.45)		10.64 (7.00)		0.003 [d]
HAM-D-29 scores					
Atypicals	31.50 (9.32)	0.35 [a]	20.00 (13.00)	0.36 [a]	0.003 [c]
Nonatypicals	27.36 (9.26)		15.18 (9.57)		0.002 [c]
Atypical scores					
Atypicals	12.25 (6.45)	0.005 [a]	7.63 (6.46)	0.40 [e]	0.02 [c]
Nonatypicals	5.18 (2.86)		5.18 (4.85)		1.00 [c]
Atypical index					
Atypicals	35.86 (9.61)	0.001 [a]	29.06 (20.75)	0.62 [a]	0.31 [c]
Nonatypicals	18.26 (9.51)		26.67 (17.68)		0.13 [c]
SERT density in the midbrain					
Atypicals	1.12 (0.14)	0.25 [a]	1.25 (0.17)	0.20 [a]	0.019 [c]
Nonatypicals	1.20 (0.13)		1.14 (0.18)		0.20 [c]
DAT density in the striatum					
Atypicals	2.55 (0.26)	0.91 [e]	2.61 (0.43)	0.16 [a]	0.63 [c]
Nonatypicals	2.53 (0.46)		2.39 (0.24)		0.22 [c]

Values are the means ± SD or numbers of subjects (percentages of the subgroup).
Abbreviations: DAT, Dopamine transporter; HAM-D, Hamilton Depression Rating Scale; SD, Standard deviation; SERT, Serotonin transporter.
[a] Student's *t*-test.
[b] Fisher's exact test.
[c] Paired samples *t*-test.
[d] Wilcoxon signed-rank test.
[e] Mann-Whitney *U*-test.

There was a significant increase in the midbrain SERT densities in the subgroup of atypicals ($t=-3.05$, $p=0.019$) but not in the subgroup of nonatypicals ($t=1.37$, $p=0.20$) during psychotherapy (Fig. 3). There were no changes in DAT densities

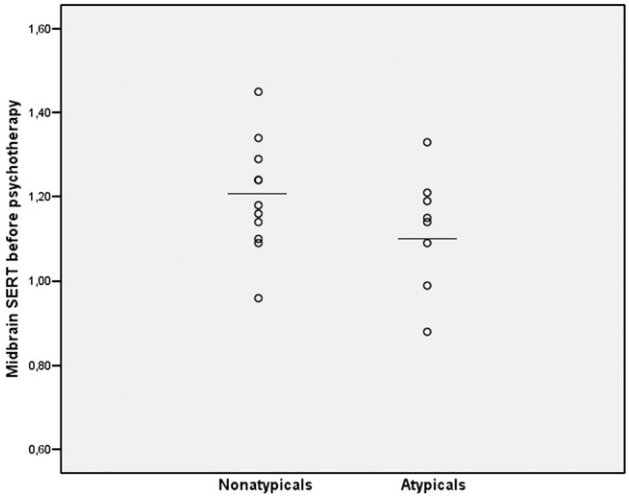

Fig. 1. Midbrain SERT before psychotherapy.

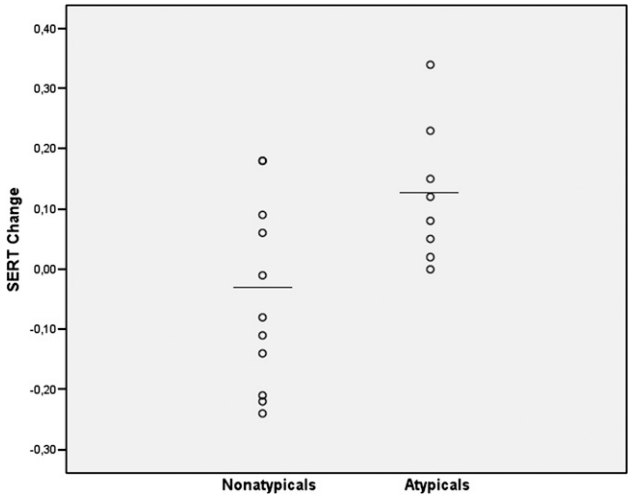

Fig. 3. The change in midbrain SERT levels during psychotherapy.

in either group ($t=-0.51$, $p=0.63$; $t=1.30$, $p=0.22$, respectively).

In the study population as a whole there were no correlations between the change in SERT levels and the change in atypical scores ($r=-0.15$, $p=0.54$) or the change in the HAM-D-21 ($r=0.37$, $p=0.12$) during psychotherapy. Furthermore, no correlations were recorded between the changes in levels of DAT and the change in atypical scores ($r=-0.16$, $p=0.51$) or the change in the HAM-D-21 ($r=0.29$, $p=0.24$). In atypicals there was a moderate but non-significant correlation between the change in SERT and both atypical scores ($r=-0.38$, $p=0.36$) and the HAM-D-21 ($r=0.48$, $p=0.23$). In the nonatypical group the correlations between the changes in SERT levels and atypical scores ($r=0.40$, $p=0.23$) and between the changes in SERT and HAM-D-21 ($\rho=0.35$, $p=0.29$) were also moderate but not significant.

In univariate ANOVA there was a difference between the subgroups in the change in midbrain SERT ($F=6.74$, $p=0.019$) but not in the change in striatum DAT ($F=1.52$, $p=0.23$). In ANCOVA with adjustment for age and gender there was a difference between the subgroups of atypicals and nonatypicals in the change in midbrain SERT ($F=6.54$, $p=0.022$) but not in the change in striatum DAT ($F=2.24$, $p=0.16$).

There were no differences between smokers and non-smokers in either the levels of SERT at baseline ($t=-0.85$, $p=0.41$) or the SERT change ($t=-0.90$, $p=0.38$). Furthermore, there were no differences in the baseline DAT ($t=-1.12$, $p=0.28$) or DAT change ($t=-0.38$, $p=0.71$). The number of smokers did not differ between the groups (Table 1).

When the three subjects who underwent spontaneous remission during the waiting period of 6 months were included in the analysis, the change in SERT showed a minor increase in significance in ANOVA ($F=7.61$, $p=0.012$) and in ANCOVA ($F=11.31$, $p=0.012$), and the respective p-values for the change in SERT during therapy were 0.008 among atypicals and 0.185 among nonatypicals.

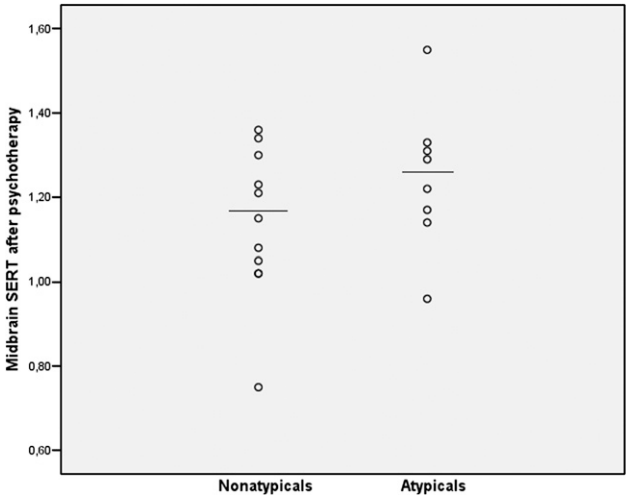

Fig. 2. Midbrain SERT after psychotherapy.

4. Discussion

To our knowledge, this was the first follow-up study on serotonin transporter availability in depressed patients during psychotherapy. Patients with ATD responded to psychotherapy with a significant elevation of midbrain SERT, whereas no change was recorded in nonatypicals. There were no changes in the levels of striatum DAT in either subgroup.

4.1. Serotonin transporters in ATD

Atypicals seemed to respond to psychotherapy with a significant increase in SERT density. Major depression has been associated with reduced SERT binding sites in the midbrain (Joensuu et al., 2007; Malison et al., 1998, Newberg et al. 2005). If decrease in midbrain SERT was to be the primary change in depression, as suggested in previous studies, it could be hypothesized that the psychotherapy-related SERT change of atypicals might be due to some unknown adaptive mechanisms inducing an increase in either the levels of SERT or serotonergic nerve terminals and therefore enhancing serotonergic activity and improving mood. However, Herold et al. (2006) observed

no differences between the depressed and the healthy controls in midbrain SERT availability by using a SERT-specific SPECT ligand [^{123}I]-ADAM. In the study of Newberg et al. (2005) there were no differences in SERT binding in the striatum and thalamus between major depressives and healthy controls. Furthermore, Meyer et al. (2004a) found increased SERT binding in major depressives with severe pessimism in the prefrontal cortex, anterior cingulate, thalamus, caudate, and putamen. The psychotherapeutic process may be emotionally challenging, and the patients may experience some distress related to the process. Increased midbrain SERT density might also be an indicator of this increased therapy-related distress. However, in the light of the observed decline in the depression scales, this seems improbable.

Higher levels of midbrain SERT have also been hypothesized to be state dependant and reflect a deficiency in extracellular 5-HT (Meyer et al., 2004a). Because of the observed elevation of SERT levels in atypicals during psychotherapy, this explanation would indicate that the serotonin levels of atypicals would actually decrease during treatment, which seems unlikely in the context of the monoamine hypothesis.

Subtype-related differential responses to psychotherapy as reflected by SERT availability could also be explained by the genetic factors modifying the expression of SERT in different subtypes of depression. Praschak-Rieder et al. (2007) reported that in the serotonin transporter-linked polymorphic region (5-HTTLPR), long polymorphism was associated with higher SERT binding in the putamen in healthy Caucasian subjects. However, Mann et al. (2000) found no association between 5-HTTLPR and SERT binding. The effect of SERT genotype on the vulnerability to depression is supported by recent literature (Pezawas et al., 2005; Vergne and Nemeroff, 2006). The genotype might also contribute to both the subtype of depression and the SERT kinetics related to the psychotherapy response, although no studies have been published on this subject.

Caspi et al. (2003) reported in a prospective longitudinal study setting that individuals with one or two copies of the short allele of the SERT promoter polymorphism exhibited more depressive symptoms and suicidality when facing stressful life events compared to those homozygous for the long allele. As mood reactivity is required for the diagnosis in the DSM-IV atypical features specifier, and higher rates of suicide attempts and frequent depressive episodes have been reported in ATD (Angst et al., 2002; Davidson et al., 1982), interesting similarities can be seen regarding the personality types and poor coping mechanisms of subjects homozygous for the long allele and patients with ATD. In a study on identical twins, Kendler et al. (1996) demonstrated that ATD is at least in part genetically determined. Similarities between the descriptions of ATD and the population with the short allele of the SERT promoter gene suggest a need for research regarding the SERT genotypes in ATD. Genetic polymorphism might contribute to certain components of the diagnostic criteria of ATD such as mood reactivity. Moreover, regardless of the similarities in recovery as measured with depression scales, atypicals might be prone to respond to the therapy process with more rapid changes in SERT levels compared to nonatypicals, possibly due to the ability to react positively to attention and care provided by the psychotherapist.

TCAs, most of which mainly have noradrenergic affinity, have been shown to be effective in treating nonatypical depression (Roose et al., 1994), whereas subjects with ATD have been shown non-responsive to TCAs (West and Dally, 1959). This lack of response to TCAs has been interpreted to support the hypothesis of a less dysfunctional noradrenergic system in ATD (Nierenberg et al., 1998). Furthermore, serotonergic transmission has been reported to be decreased in ATD (Asnis et al., 1995). These findings may indicate that the recovery-related alterations in the neurotransmitter transporter levels of nonatypicals could be seen more prominently in noradrenergic transporters (NORT), and not in SERT. However, we were not able to record NORT densities with our radioligand.

4.2. Serotonin transporters and the severity of depression in ATD

Our previous article with a cross-sectional setting reported an inverse correlation between midbrain SERT densities and atypical scores in all depressed subjects, whereas no such correlation was seen between midbrain SERT and HAM-D-21 scores (Lehto et al., 2006). Thus, a correlation between recovery as measured by atypical scores and the change in SERT densities might have been expected in this follow-up study. However, the correlations between the change in SERT and the changes in depression scores were non-significant in both groups, although interestingly a trend towards an inverse correlation between the SERT change and atypical measures was seen in atypicals, and the reverse was observed in nonatypicals. The number of cases was rather limited, and the correlation between the changes in SERT levels and atypical measures might therefore have reached significance with a larger number of study subjects. Several confounding factors may also have contributed to this result. The validity of the diagnostic criteria of ATD has been under debate since its first appearance in the scientific literature (Benazzi, 2002; Matza et al., 2003; Parker and Crawford, 2007; Quitkin et al., 1988; Quitkin, 2002), and it is has been proposed to be a multi-dimensional disorder crossing the borders between DSM-IV Axis I and Axis II by mixing both symptom states and personality-related features (Parker and Thase, 2007). This setting creates a dilemma for research on the biological features of ATD, as some specific features of the diagnostic criteria may associate with certain biological variables. Analysis of such associations would require fairly large study populations.

4.3. The effect of psychotherapy

Mercier et al. (1992) observed that atypicals responded to CT. In our sample, both atypicals and nonatypicals responded to psychodynamic psychotherapy with a similar decline in HAM-D-29 scores, and there was no difference in the response rates between the two groups. These results are in concordance with the findings of Stewart et al. (1998), who reported no differences in depression scales in response to CT or IPT

between depressive subtypes. The duration of treatment in previous studies on the efficacy of psychotherapy with atypically depressed subjects has ranged from 10 to 16 weeks in three studies (Jarrett et al., 1999; Mercier et al., 1992; Stewart et al., 1998), and in one study there was a total of 8 months of psychotherapy (Jarrett et al., 2000). As far as we are aware, the duration of psychotherapy intervention in our study was longer than in any previous study on subjects with ATD, which can be considered a strength.

The psychotherapy-induced plastic changes in the human brain as reflected by alterations in the functions of certain neural systems remain heterogeneous (Linden, 2006). Moreover, the unclear relationship between imaging findings, diagnostic measures and their interdependency in relation to the course of time and course of illness factors further adds to the difficulties in interpreting the findings. When performing further analysis including the three subjects who underwent spontaneous remission during the waiting period of 6 months, we noticed that their SERT levels behaved in a similar manner to those of subjects who either started the therapy immediately or remained depressed throughout the waiting period. This, as well as the finding of midbrain SERT elevation in atypicals, may indicate that the changes in neurotransmitter transporter levels do not reflect the degree of clinical depression as measured with depression scales. Clinical recovery during psychotherapy reflects alterations in complex neural networks, and the alterations in SERT levels seem to function at least to some degree independently from clinical depression. Naturally, the alterations in the levels of SERT need to be considered as only a part of the psychotherapy-induced changes in the brain.

4.4. Limitations

Significant comorbidity has been reported between atypical depressive states and bipolar mood disorder. Akiskal et al. (2006) reported that 75.7% of their subjects with ATD met the criteria for bipolar disorder, mainly type II. No differences have been observed in SERT levels between patients with bipolar and unipolar depression (Oquendo et al., 2007). Previously, our group reported higher SERT binding during the mixed hypomanic state in one study subject in a case-control study (Tolmunen et al., 2004). In that study, elevated levels of midbrain SERT normalized during eight months of psychodynamic psychotherapy. Due to the high degree of comorbidity, some of the subjects in the current study might have developed the hypomanic state, which would have affected our results. However, there was no evidence of bipolar spectrum disorders in any of the study subjects in the baseline clinical evaluation. Furthermore, the study subjects had psychotherapy sessions twice weekly and were thus under close clinical observation by a trained psychotherapist. None of the subjects were reported to have developed hypomania or a mixed state during the follow-up period.

Because our study setting (i.e. having waiting-list controls) related to other dimensions of the MAP*Psy study, some of our subjects recovered spontaneously during the waiting period of six months. As Gold et al. (1988) reported, the duration of major depression episodes ranges from approximately 7 to 14 months. Furthermore, Keller et al. (1992) showed in a naturalistic study setting that 50% of depressed subjects recover during a follow-up of six months. Based on these findings, our subjects can be considered to represent an average depressed population. After the necessary exclusions due to spontaneous recovery, there were eight atypicals and five nonatypicals in TG-1, while TG-2 comprised six nonatypicals. The different distribution of atypical and nonatypical subjects in therapy groups and the waiting period of six months prior to the initiation of therapy in TG-2 might have created bias on our results. However, the duration of depressive episodes prior to admission to the study already varied between subjects, regardless of the inclusion in a particular group, and there were no significant differences in SERT levels between subjects in TG-1 and TG-2 at baseline.

The nucleus coeruleus, with noradrenergic cell bodies, is located close to our midbrain ROI. Thus, we cannot completely exclude the possibility of nor-β-cit binding to the noradrenergic transporters (NORT) and thus biasing our findings. The substantia nigra, consisting mainly of dopamine cell bodies, is also located close to our target region. The B-CIT derivatives have previously been reported to exhibit similar selectivity for serotonin and dopamine transporters (Laruelle et al., 1994; Carroll et al., 1995). However, the resolution of the utilized imaging method is considered to prevent DAT signals in a reliable manner, eliminating the possible bias in our results concerning SERT densities. Furthermore, Hiltunen et al., (1998) reported that nor-β-CIT has a 33% higher SERT specific binding capacity compared to the previously utilized β-CIT radioligand.

5. Conclusions

This was the first follow-up study to investigate alterations in neurotransmitter transporter levels in depressed subjects. While all subjects showed a significant decline in symptoms after one year of psychotherapy as measured with depression scales, a significant increase in SERT levels was seen only in atypical study subjects. DAT levels remained similar in both groups. The psychotherapy-related SERT elevation of atypically depressed subjects may be due to some unknown adaptive mechanisms inducing an increase in either the levels of SERT or serotonergic nerve terminals and therefore enhancing serotonergic activity and improving mood. If these assumptions were to be confirmed by future studies, it might be postulated that the physiological changes induced by psychotherapy are similar to those of serotonergic antidepressants.

6. Contributors

SML wrote this report and interpreted the data. TT planned the study and analyzed and interpreted the data. MJ and MV-K also interpreted the data. PIS participated in the initiation and planning of the study. RV was responsible for the MRI scans and the interpretation of the scans. PA participated in the clinical study of the patients. JT participated in the analyses and

interpretation of the data. JK performed SPECT analyses. JL initiated and planned the study project on the brain imaging of depressed patients and their psychotherapy treatment. All authors read, critically revised and approved the final manuscript.

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