Psychological Medicine (2011), **41**, 419–429. © Cambridge University Press 2010
doi:10.1017/S0033291710000486

ORIGINAL ARTICLE

Serotonin and dopamine transporters in relation to neuropsychological functioning, personality traits and mood in young adult healthy subjects

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Background. Serotonin and dopamine neurotransmitter systems are implicated in the regulation of mood, cognition and personality traits and their dysfunction is thought to be implicated in diverse psychopathologies. However, in healthy subjects the relationship between the serotonin and dopamine systems and neuropsychological functioning and personality traits is not clearly established. In the present study we investigated whether neuropsychological functioning, personality traits and mood states of a group of healthy subjects are associated with *in vivo* measures of serotonin transporters (SERTs) and dopamine transporters (DATs).

Method. A total of 188 young healthy subjects underwent neuropsychological and subjective measurements of memory function, depression and impulsivity. Participants' SERT and DAT availability in predefined regions of interest were assessed using single photon emission computed tomography (SPECT) with the radiotracer [^{123}I]β-CIT. Individual magnetic resonance imaging (MRI) scans served as anatomic reference.

Results. We did not find any significant association between SERT or DAT availability and neuropsychological test performance or self-reported impulsivity and mood. There were no significant sex differences in SERT or DAT availability, but men performed significantly better on some tests of visuospatial functioning than women.

Conclusions. Robust negative findings for striatal DAT availability seriously question earlier findings of positive associations between DAT availability and cognitive functions in healthy subjects. Our results also suggest that subcortical SERT availability is not associated with the neuropsychological functions and personality traits assessed. In summary, the present study suggests that neuropsychological and personality measurements in young healthy people are not associated with subcortical SERT or striatal DAT availabilities in the brain.

Received 9 January 2009; Revised 27 January 2010; Accepted 9 February 2010; First published online 6 April 2010

Key words: Dopamine transporter, healthy controls, neuropsychological functioning, serotonin transporter, SPECT.

Introduction

It has been suggested that the neurotransmission of both serotonin and dopamine plays a role in personality traits, mood states and neuropsychological functioning. Consequently, dysfunction of the serotonergic and/or dopaminergic system is thought to be implicated in diverse psychopathologies, for example depression, schizophrenia, obsessive–compulsive disorder and impulsivity-related disorders such as attention deficit hyperactivity disorder (ADHD) (Aouizerate *et al*. 2005; Hariri & Holmes, 2006; Gudelsky & Yamamoto, 2008; Oades, 2008; Pattij & Vanderschuren, 2008; Zhu & Reith, 2008; Howes & Kapur, 2009). Dopamine has been linked to neuropsychological functions such as selective attention, working memory and motivational functions (Robbins & Roberts, 2007). Furthermore, antidepressant drugs such as selective serotonin reuptake inhibitors (SSRIs) may enhance cognitive functioning and learning abilities, which points to the involvement of serotonin in learning and memory (Meneses, 1999). Personality traits and neuropsychological abilities refer to functional patterns that differ among individuals. They are thought to be, in part, heritable (Cloninger, 1987;

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Edmonds *et al*. 2008; Friedman *et al*. 2008), and several associations have been reported with factors related to neurotransmission, for example polymorphisms in the serotonin transporter gene (5-HTTLPR) (Hariri & Holmes, 2006; Roiser *et al*. 2006). The central question emerging from these findings is whether *in vivo* assessment of neurotransmitter systems allows us to make predictions about cognition, self-reported mood states and personality traits.

The serotonin transporter (SERT) and dopamine transporter (DAT) are expressed exclusively in the membrane of serotonergic and dopaminergic neurons respectively, and regulate intrasynaptic neurotransmitter levels. The homeostatic tone of neurotransmitter systems is reflected by transporter concentration (Stahl, 2000). Positron emission tomography (PET) and single photon emission computed tomography (SPECT) enable us to quantify the *in vivo* availability of central SERTs and DATs.

So far, only a few studies have investigated the relationship between markers of serotonergic/dopaminergic transmission and cognition, mood and personality in healthy subjects, and have yielded inconsistent results (Mozley *et al*. 2001; Suhara *et al*. 2001; Takano *et al*. 2007; Borg *et al*. 2009; Kalbitzer *et al*. 2009; Tsai *et al*. 2009). Takano *et al*. (2007) demonstrated a positive correlation between the neuroticism personality trait and thalamic SERT binding in healthy subjects. Kalbitzer *et al*. (2009) found the personality trait 'openness to experience', with high scores being indicative of cognitive flexibility and openness to change, to be associated with lower SERT binding in the midbrain, putamen and thalamus. In another study, 'novelty seeking' was correlated negatively with D_2 receptors in the right insular cortex (Suhara *et al*. 2001). Mozley *et al*. (2001) have provided the only report on significant associations between striatal DAT availability and memory in healthy controls. Conversely, Borg *et al*. (2009) did not find any association of neuropsychological test scores and serotonin receptor ($5\text{-}HT_{1A}$) density, but reported a relationship between performance on the Wisconsin Card Sorting Test and the 5-HTTLPR genotype. Finally, a study by McCann *et al*. (2008) compared 2-week-abstinent 3,4-methylenedioxy-*N*-methamphetamine (MDMA; 'ecstasy') users and healthy controls on DAT and SERT availability and the association with performance on neuropsychological tests. In the controls, lower SERT availability in the dorsolateral prefrontal cortex and parietal cortex was associated with poorer performance on several memory tasks and the Digit Span Scale.

Studies that looked at personality traits in cohorts that also included psychiatric patients have consistently shown evidence for associations between DAT/SERT and neuropsychological or personality disturbances, but the direction of association remains conflicting. For example, impulsivity is thought to play a role in several psychopathologies, including ADHD and impulsive suicidal behavior. In some studies, impulsivity was found to be associated with lower SERT binding (Lindström *et al*. 2004; Ryding *et al*. 2006) and higher DAT availability (Tiihonen *et al*. 1997) whereas another study found associations in the opposite direction (Koch *et al*. 2007). Similarly, SERT alterations have often been reported in mood disorders (Ichimiya *et al*. 2002; Meyer *et al*. 2004; Parsey *et al*. 2006). High scores on depression rating scales were associated with low SERT binding in depressed patients (Newberg *et al*. 2005; Joensuu *et al*. 2007; Lehto *et al*. 2008*a*), but others could not replicate these findings (Koch *et al*. 2007) or found associations in the opposite direction (Ichimiya *et al*. 2002; Meyer *et al*. 2004). Finally, neuroimaging studies investigating drug-induced neurotoxic effects on cognition have found correlations between memory task performances and monoamine transporter availability (DAT and vesicular monoamine transporter) in the striatum of current and former MDMA and *N*-methyl-phenylpropylamine (methamphetamine) users (Johanson *et al*. 2006; Schilt *et al*. 2007; de Win *et al*. 2008; McCann *et al*. 2008).

Overall, there are large inconsistencies in, and especially in the direction of, possible associations of central DAT and SERT concentrations and the expression of particular personality traits, mood states and neuropsychological functions. This is especially true for studies in subjects without clinically relevant psychopathology. The aim of this study was therefore to resolve this problem of inconsistent findings by examining a much larger sample of young healthy subjects than those that were studied before, using both neuropsychological tasks and mood and personality self-reports in a study simultaneously looking at SERT and DAT.

Method

Subjects

A group of healthy young adults (aged 18–24 years, 111 females, 77 males) was recruited between 2002 and 2004. These subjects had participated in The Netherlands XTC Toxicity (NeXT) Study, of which a detailed description can be found elsewhere (de Win *et al*. 2005*b*). Participants were actively recruited (de Win *et al*. 2005*b*) and they were ecstasy-naive at the time of recruitment. The main criterion for inclusion was intent (probable or certain) to use ecstasy in the near future for the first time. Exclusion criteria

https://doi.org/10.1017/S0033291710000486 Published online by Cambridge University Press

were age <18 or >35 years, ecstasy use in the past, severe physical or mental illness, use of psychotropic medications (e.g. SSRIs), pregnancy and intravenous drug use. Subjects had to abstain from psychoactive substances for at least 2 weeks and from alcohol for at least 1 week before examinations. This was checked in urine (enzyme-multiplied immunoassay for amphetamines, MDMA, opioids, cocaine, benzodiazepine, cannabis, and alcohol). The study was approved by the medical ethics committee of the Academic Medical Center, University of Amsterdam. All subjects gave written informed consent and received a reimbursement for their participation.

Neuropsychological tests and personality questionnaires

A detailed description of the tests and questionnaires that were used can be found elsewhere (Schilt *et al*. 2007).

Cognition

Attention and working memory. The Paced Auditory Serial Addition Test (PASAT; Gronwall, 1977) measures working memory and arithmetical skills (maximum score 60). The Digit Span Scale (DSS), a subtest of the Wechsler Adult Intelligent Scale – Revised (WAIS-R; Wechsler, 1981), measures working memory capacity (maximum score 21). The Rey Auditory Verbal Learning Test (RAVLT; Rey, 1964; Van den Burg *et al*. 1985) measures verbal memory in terms of recalling a list of 15 words (maximum score 75, after five trials), delayed recall (maximum score 15, after 20 min), and recognition (maximum score 30).

Visual memory and visuospatial function. A computerized adaptation of the Memory for Designs Test (MFDT; Graham & Kendall, 1960) was used to test visual memory in terms of number of correctly reproduced elements (maximum score 105, after five trials) and delayed (maximum score 21, after 15 min) reproduction. In the Mental Rotation Test (Shepard & Metzler, 1971), subjects must judge whether 20 pairs of block designs, drawn from different perspectives, were identical or different (maximum 40 hits, maximum time 6 min). A computerized adaptation of the Judgment of Line Orientation task (JoLO; Benton *et al*. 1987) was used to test visuospatial functioning. Subjects are required to identify which two of 11 lines, presented in a semicircular array, have the same orientation in a two-dimensional (2D) space (maximum score 30).

Impulsivity, decision making and risk-taking behavior. A computerized version of the Iowa Gambling Task (IGT; Bechara *et al*. 1994, 1999) was used to measure decision making and risk-taking behavior. The explicit goal of the test is to maximize profit on a loan of play money (Bechara *et al*. 2000) (maximum score 60).

Intelligent quotient. Verbal intelligence was estimated with the Dutch Adult Reading Test (DART; Schmand *et al*. 1991), a Dutch version of the National Adult Reading Test (NART; Nelson & O'Connell, 1978).

Personality

The 31-item Dutch version of the Barratt Impulsiveness Scale, version 11 (BIS-11), scored on a four-point scale, was used as a measure of self-reported impulsivity (Patton *et al*. 1995), with subscales representing attentional, motor and non-planning impulsivity. The Spanningsbehoefte lijst (SBL), the 51-item Dutch adaptation of the Sensation Seeking Scale (Zuckerman & Link, 1968), was used to measure sensation seeking (Feij *et al*. 1982). A general sensation seeking score (scored from 1 to 5), the sum of the subscales 'thrill and adventure seeking' (TAS), 'experience seeking' (ES), 'boredom susceptibility' (BS) and 'disinhibition' (DIS), was calculated.

Mood

Depression. Current depressive symptoms were assessed using the 21-item Beck Depression Inventory (BDI; Beck *et al*. 1961), with higher scores indicating more depressive symptoms (maximum score 63).

SPECT and magnetic resonance imaging (MRI)

Acquisition. SPECT was used for quantifying subcortical SERT and striatal DAT availabilities (Reneman *et al*. 2001*a*, *b*). Subjects were intravenously injected with approximately 4 mCi (140 MBq) of [^{123}I]β-CIT. SPECT imaging was performed with a brain-dedicated 12-detector single-slice scanner (Strichman Medical Equipment 810, Inc., USA). Scanning was started 4 h post-injection (p.i.) when specific binding to SERT is stable (Pirker *et al*. 2000). A second scan, at 24 h p.i., was accomplished to measure DAT availability. At this time-point stable specific binding to striatal DAT is reached (Laruelle *et al*. 1994). Further acquisition parameters were as described previously (de Win *et al*. 2005*a*).

For anatomic reference, T1-3D MRI was performed using a 1.5-T scanner (Signa Horizon, LX 9.0, General Electric Medical Systems, USA), as described previously (de Win *et al*. 2007).

Post-processing. On all SPECT images, attenuation correction was performed and all images were

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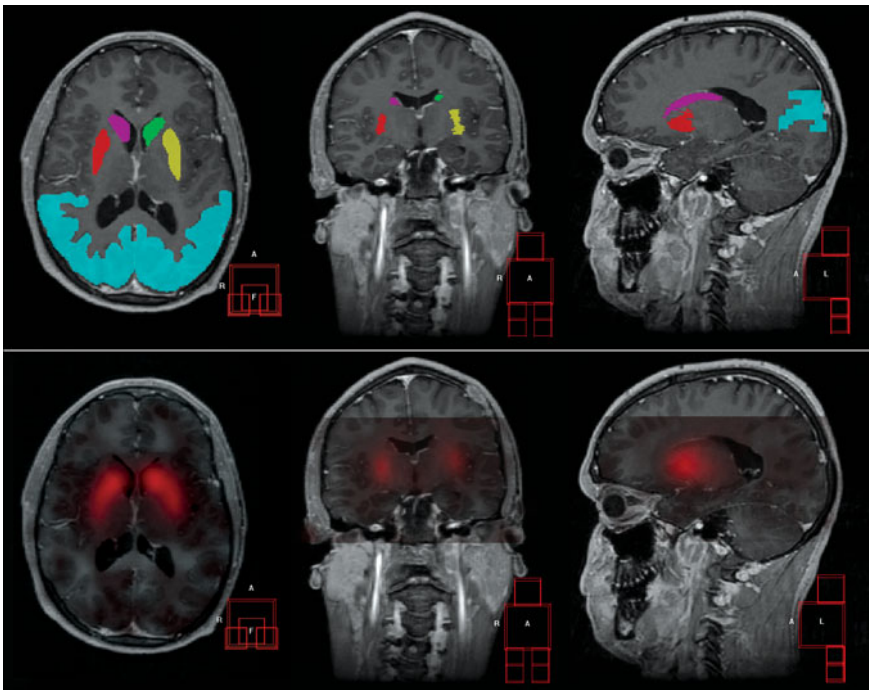

Fig. 1. An example of region of interest (ROI) drawings to analyze dopamine transporter (DAT) availability and match of magnetic resonance imaging (MRI) image with single photon emission computed tomography (SPECT) image. From left to right: axial, coronal, sagittal views. Upper row: five three-dimensional (3D) ROIs drawn on individual MRI scans: caudate nucleus (green, violet), putamen (yellow, red), occipital cortex (light blue). Lower row: individual SPECT scans matched on individual MRI scans; intensity of uptake value indicated by intensity of red scaling.

reconstructed in 3D mode. Quantitative analyses of SERT availability has been described previously by de Win *et al*. (2008). In brief, each individual SPECT and MRI scan was registered and then co-registered to the 152 MNI brain. For the analysis of SERT availability, regions of interest (ROIs) were drawn on the MNI template in the midbrain and thalamus, and then overlaid over each co-registered SPECT scan. Specific to non-specific binding ratios for SERT were calculated using the following formula: [(activity in ROI) – (cerebellar activity)/(cerebellar activity; non-displaceable binding potential; BP_{ND})] (Innis *et al*. 2007).

For the analysis of striatal DAT availability, ROIs were drawn on each individual T1-3D MRI scan for the caudate nucleus (bilaterally), the putamen (bilaterally) and the occipital cortex, which was assumed to represent non-displaceable activity (reference region). ROIs were drawn by making use of self-developed software (van Herk *et al*. 2000). The choice of ROIs was restricted to the subcortical and striatal brain areas because of their dense DAT and SERT innervations. By contrast, cortical brain regions only show low DAT and SERT densities, and were not included in the ROI analysis. Using the same program, we matched the SPECT scans of the subjects with their individual T1-3D MRI scans, and extracted DAT availability of the respective ROIs (Fig. 1). Specific to non-specific binding ratios for DAT were calculated as: [(activity in ROI) – (activity in occipital cortex)/(activity in occipital cortex; BP_{ND})] (Innis *et al*. 2007).

Statistical analyses

Whether SERT/DAT availability in a specific brain region predicts the performance on a neuropsychological test, personality questionnaire or mood questionnaire was tested by means of linear regression analysis, using SPSS version 16.0 (SPSS Inc., USA). BP_{ND} for different regions (midbrain, thalamus, caudate nucleus or putamen) was taken as the independent variable and test scores were chosen as the dependent variables. We corrected for age and gender as these factors are known to influence SERT and DAT availability (van Dyck *et al*. 2000; Mozley *et al*. 2001). The analyses with neuropsychological test scores as dependent variables were additionally corrected for IQ. As determined by Bonferroni correction, p values were considered statistically significant at a level of $p = 0.005$ to correct for multiple testing for the 10 main tests on neuropsychological functioning, personality and mood. The different ROIs were not included as variables in the Bonferroni correction because regional

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SERT or DAT expression levels are highly interdependent. Effect sizes were calculated for DAT and SERT separately, with an α level of 0.05, 80% power, and four predictors (one test/questionnaire, IQ, age and gender). The minimal detectable effect size for DAT ($n=79$) was $r^2=0.1388$ ($r=0.3725$), and for SERT ($n=188$) it was $r^2=0.0612$ ($r=0.2474$). From these calculations, it could be expected that even small correlations between the parameters could be detected with the current sample sizes and the applied significant levels. We checked for potential sex differences by means of a t test, and looked for possible age effects by means of correlational analyses. Because study participants were selected on the basis of a relatively high probability of starting to use ecstasy, substance-abuse parameters were screened for potential confounding effects. Nicotine, alcohol, cannabis, cocaine and amphetamine use was assessed dichotomously (ever used/not used), and alcohol, nicotine and cannabis intake was checked additionally in more detail by asking for frequency of use. Potential confounders were defined as variables that were associated with one of the dependent variables (SERT or DAT availability) at the $p<0.10$ level of significance (Hosmer & Lemeshow, 2001).

Results

All 188 participants completed the mood questionnaire, 187 completed the personality questionnaires, and 184 completed all neuropsychological tests. The IGT was accomplished by 149 subjects. Only 177 SERT scans could be analyzed because 11 participants had to be excluded from analysis due to problems with scanning or matching. Of these 177 subjects, 80 also participated in DAT imaging, but one subject had to be excluded from analysis because of poor scan quality. Demographic data, data on SERT and DAT availability, neuropsychological measures (mean score and standard deviation), and substance use characteristics are presented in Table 1.

The results of the regression analysis on the SERT data revealed no significant associations between SERT availability in any of the selected brain regions and performance on any of the neuropsychological tests, personality scores or mood questionnaires. Although there were some trends for significance (Table 2; effects with $p<0.1$ are shown), no overall effect pattern could be observed. The only significant ($p=0.045$, uncorrected) predictor for SERT binding potential in the midbrain was performance on the RAVLT, sum trial 1–5. However, this association was no longer significant after Bonferroni correction. The regression analysis of the DAT data also revealed no significant associations between DAT availability in the striatum and neuropsychological test performance, personality questionnaire scores and mood ratings (Table 2).

Supplementary Table S1 (available online) presents all correlations performed of DAT or SERT availability with neuropsychological test or questionnaire (age, gender and IQ as control variables).

Checking for potential sex differences within the sample (Table 1), men and women showed no differences in their SERT and DAT availability in the different brain areas. No differences between men and women were also found with respect to neuropsychological test performances, except for the Mental Rotation Test ($p<0.001$) and the JoLO test ($p=0.006$; no longer significant after Bonferroni correction). Men performed slightly better on these visuospatial functioning tests. Significant sex differences were also found for the Sensation Seeking Scale, with men scoring higher than women ($p=0.003$). Men (mean 106.6, S.D. = 10.0) also had a significantly ($p=0.001$) higher estimated DART-IQ compared to women (mean 102.0, S.D. = 8.3). We checked for a possible age-dependent decline in DAT or SERT availability but we did not find any effects of age in our sample.

The only possible substance-abuse confounder was the amount of alcoholic drinks per week ($r=-0.18$, $p=0.017$ for SERT availability in the thalamus; $n=176$). One subject was excluded from this analysis because of inconsistent reporting on alcohol consumption. When alcohol consumption was added to the regression analysis, only small and non-relevant changes were observed: midbrain and RAVLT sum trial 1–5 ($\beta=-0.154$, $p=0.048$), midbrain and RAVLT recall ($\beta=-0.130$, $p=0.093$); thalamus and IGT ($\beta=-0.178$, $p=0.044$); right caudate nucleus and PASAT 1.6 ($\beta=0.222$, $p=0.041$); right caudate nucleus and MFDT sum score trial 1–5 ($\beta=0.194$, $p=0.065$). None of these associations remained significant after correction for multiple testing.

Discussion

The purpose of this study was to assess the association of *in vivo* SERT and DAT availability with personality traits, mood state and neuropsychological abilities in a large group of healthy young adults. We could not replicate any of the previously reported associations between neuropsychological, mood or personality measures and SERT or DAT in healthy people. Even when taking trends for significance into account, no effect pattern, with, for example, one particular cognitive domain related to DAT or SERT, could be identified. The overall conclusion of our analyses is that no such association exists in our study sample.

Table 1. *Subject characteristics: demographics, SERT and DAT availability, self-reported personality and mood measures, neuropsychological test scores and substance use*

	Mean (S.D.)	*n* (female/male)	*t* sex difference	*p* value sex difference
Age (years)	21.3 (3.0)	188 (111/77)	1.160	0.248
Years of education	14.2 (2.2)	188 (111/77)	−0.935	0.351
DART-IQ	103.9 (9.3)	188 (111/77)	3.446	0.001*
SERT availability (BP_{ND})		177 (105/70)		
Midbrain	1.3 (0.4)		−1.044	0.298
Thalamus	1.3 (0.4)		−1.600	0.111
DAT availability (BP_{ND})		79 (48/31)		
Caudate nucleus	8.9 (2.3)		1.608	0.112
Putamen	10.6 (2.2)		1.003	0.319
Beck Depression Inventory	3.5 (3.5)	188 (111/77)	−1.256	0.211
Barratt Impulsiveness Scale	68.1 (9.2)	188 (111/77)	1.426	0.156
Sensation Seeking Scale	13.6 (1.5)	187 (110/77)	3.054	0.003*
Paced Auditory Serial Addition Test		188 (111/77)		
1.6 s	42.2 (7.9)		1.112	0.268
2.4 s	51.8 (6.5)		−1.890	0.060
Digit Span Scale		188 (111/77)		
Forward	14.9 (2.6)		−1.689	0.093
Backward	11.3 (2.4)		−1.037	0.301
Rey Auditory Verbal Learning Test		188 (111/77)		
Sum score trial 1–5	58.2 (6.0)		−0.716	0.475
Recall	13.5 (1.6)		−0.351	0.726
Recognition	29.9 (0.3)		0.995	0.321
Memory for Design Test		188 (111/77)		
Sum score trial 1–5	94.3 (8.7)		1.563	0.120
Recall	20.7 (0.8)		0.637	0.525
Mental Rotation Test	22.7 (7.0)	188 (111/77)	6.208	0.000*
Judgment of Line Orientation Test	22.6 (3.8)	188 (111/77)	3.083	0.002*
Iowa Gambling Task		149 (86/63)		
Total good–bad deck choices	8.5 (21.7)		0.432	0.666
Nicotine (packs of cigarettes/week)	1.3 (2.4)	188		
Nicotine (ever used)		149		
Alcohol (units/week)	11.3 (9.5)	188		
Alcohol (ever used)		186		
Cannabis (joints/week)	0.8 (2.0)	188		
Cannabis (ever used)		161		
Amphetamine (ever used)		13		
Cocaine (ever used)		25		

SERT, Serotonin transporter; DAT, dopamine transporter; DART, the Dutch Adult Reading Test; BP_{ND}, non-displaceable binding potential; S.D., standard deviation.

*Statistically significant with $\alpha = 0.01$ (uncorrected).

In contrast to our findings, a few studies looking for an association between neurotransmitter systems and cognition or personality measurements in healthy subjects were able to demonstrate such a relationship, whereas others did not find such associations. These inconsistent results may have emerged from differences in study population, such as sex and age differences, or from other methodological issues such as the use of different, or too insensitive, tests and questionnaires and differences in the application of corrections for multiple testing. When we compare the results of these studies to the present one, a major difference is the sample size, with our sample being by far the largest to date. Whereas our study tested up to 177 SERT and 79 DAT subjects, the study with the largest sample size reporting a significant association

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Table 2. *Results of the regression analysis: SERT or DAT availability in different brain areas and performance on neuropsychological tests, mood and personality questionnaires. Results with $p<0.1$ are shown*

ROI	Test	β	r	t	p value	n
SERT						
Midbrain	RAVLT sum score trial 1–5	−0.153	−0.153	−2.019	0.045	177
	RAVLT recall	−0.144	−0.143	−1.887	0.061	
Thalamus	IGT	−0.159	−0.155	−1.825	0.070	
DAT						
Right caudate nucleus	PASAT 1.6	0.182	0.195	1.711	0.091	79
	MFDT, sum score trial 1–5	0.198	0.221	1.949	0.055	

SERT, Serotonin transporter; DAT, dopamine transporter; ROI, Region of interest; β, standardized beta; r, correlation coefficient; RAVLT, Rey Auditory Verbal Learning Test; IGT, Iowa Gambling Task; PASAT 1.6, Paced Auditory Serial Addition Test 1.6; MFDT, Memory for Design Test.

is the one by Mozley *et al*. (2001), in which, using [^{99m}Tc]TRODAT-1 SPECT, 66 subjects were tested for possible associations between DATs and memory in healthy subjects. They used the Pennsylvania Verbal Learning Test, a variant of the RAVLT that we used. In contrast to our findings, they reported significant correlations between DATs and performance scores: $r=0.43$, $p=0.02$ in men (caudate nucleus) and $r=0.40$, $p=0.02$ in women (caudate nucleus, putamen). Methodological differences may be responsible for the differential findings. For example, Mozley *et al*. used a fixed-ROI template (i.e. without co-registration of individual MRIs) and images were acquired at 3 h p.i., whereas 4.5–5 h p.i. is probably a better time-point to analyze DATs with TRODAT SPECT (Acton *et al*. 2000). Moreover, a single [^{123}I]β-CIT SPECT scan at 24 h p.i. is well validated to assess striatal DAT availability (Laruelle *et al*. 1994) and considered superior to [^{99m}Tc]TRODAT-1 SPECT. Finally, Mozley *et al*. (2001) did not correct their findings for multiple testing, and therefore their reported associations between DAT availability and memory performance might be a false-positive (chance) finding.

Apart from the differences in sample size and radioligand use, there were differences with respect to tests used to investigate neuropsychological performance and personality traits. In their [^{11}C]DASB PET study, Takano *et al*. (2007) found that higher thalamic SERT binding correlated to higher levels of neuroticism and depressive feelings, measured with the NEO personality inventory. It should be noted that they were not able to find any association with NEO impulsivity, which is in agreement with our study finding of no association between impulsivity scores and SERT availability.

A recent [^{11}C]DASB PET study (Kalbitzer *et al*. 2009), testing 50 healthy subjects, found 'openness to experience', a subscale of the NEO, to be associated with lower SERT binding in the SERT-rich midbrain, putamen and thalamus. Notably, the authors do not mention associations with any of the other NEO subscales, such as the neuroticism facet, for which the study by Takano *et al*. (2007) found significant associations. Takano *et al*. also did not report an association with the NEO openness to experience subscale.

Another [^{11}C]DASB PET study (McCann *et al*. 2008) investigated a group of 2-week abstinent MDMA users ($n=16$) and healthy controls ($n=16$). When all subjects were included for a correlational analysis, lower SERT-binding potentials in the dorsolateral prefrontal cortex and parietal cortex were associated with poorer performance on the Wechsler memory scale and the DSS. After splitting the group, and in contrast to what would be expected, this association remained strong only for the control group and not for the former MDMA users. We did not find any association between the DSS and SERT in our sample; however, we only assessed SERT in subcortical brain areas that express SERT intensively.

It might be thought that we failed to replicate previous findings because we used SPECT instead of PET. However, it should be noted that we were not able to replicate the positive [^{99m}Tc]TRODAT SPECT association with memory dysfunction (Mozley *et al*. 2001) in our study even though we had a larger sample, used the radioligand [^{123}I]β-CIT, and applied individually co-registered MR images, ensuring high reliability of quantification. The other three out of four studies reporting positive findings in healthy subjects used PET and the selective SERT radiotracer [^{11}C]DASB (Takano *et al*. 2007; McCann *et al*. 2008; Kalbitzer *et al*. 2009). Although, the reliability of [^{123}I]β-CIT SPECT in quantifying DAT and SERT is generally accepted (Seibyl *et al*. 1996; Pirker *et al*. 2000; de Win *et al*. 2005*a*), the sensitivity and specificity of this technique (especially for measuring SERT in cortical

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areas) are lower compared to [^{11}C]DASB PET, supporting the reported positive findings of the three [^{11}C]DASB PET studies.

Another reason for the inconsistency of our findings with previous studies might be the variation within the samples. It might be that the variation in test scores or SERT/DAT binding values in this study were too small to find effects. Where possible, we checked whether our sample deviated from normal population scores (Feij *et al*. 1982; Patton *et al*. 1995; Zuckerman & Kuhlman, 2000; Beck *et al*. 2002). Subjects from the present study scored within a normal range on measures of depression, impulsivity and sensation seeking. Moreover, variance and distribution of SERT and DAT availability values were comparable to that of healthy subjects of other studies (Maron *et al*. 2004; Joensuu *et al*. 2007; Lehto *et al*. 2008*b*; van der Wee *et al*. 2008).

Another reason why the small studies with healthy subjects did find associations between neuropsychological measures and DAT or SERT could be that they did not rigorously correct for multiple testing. Only Takano *et al*. (2007) reported a conservative p value ($p<0.008$), whereas others (Mozley *et al*. 2001; Kalbitzer *et al*. 2009) chose not to correct for multiple testing. In the present study, p values were considered statistically significant at a level of $p<0.005$ to correct for multiple testing for the 10 main tests and questionnaires. This correction might be regarded as too conservative. However, a less conservative correction contributes to the chance of false-positive findings.

Overall, we can say that the positive findings that have been reported on neuropsychological functioning and personality traits and SERT and DAT availability in healthy subjects are difficult to replicate in our present study. The main reasons are probably differences in assessment instruments (e.g. only a few cognitive assessments were computerized, and consequently were less precise than in previous studies), differences in the SERT and DAT availability measurements (PET *versus* SPECT) and the application of corrections for multiple testing.

Although our large sample size definitely contributed to statistical power, one weakness lies in a possibly biased study population. Subjects were selected on the basis of their relatively high probability of starting to use ecstasy in the future. This selection might pose a limitation to the external validity of the study, because the study subject population had higher levels of substance use than the general population. Using this selection criterion, we may have selected for individuals who had more self-control (and less impulsivity) because they were tempted, but had not tried, ecstasy. However, the impact of this selection was probably very small, because mean test scores and variances in outcome measures in the present study were highly comparable to other, less selective, healthy populations. Furthermore, statistical analysis showed that substance-abuse parameters did not affect DAT or SERT availability significantly. In the present sample of 188 subjects, substance use was fairly limited (1.3 packs of cigarettes/week, S.D. = 2.4; and 0.8 joints/week, S.D. = 2.0), and only a minority of participants had ever used amphetamines ($n=13$) or cocaine ($n=25$). None of the subjects met the criteria for drug abuse. Urine tests confirmed that none of the subjects had used drugs of abuse in the two weeks before they were scanned. The only identified potential confounder, with fairly small effects, was alcohol consumption (mean 11.1 units/week, S.D. = 8.9). Overall, we cannot rule out any effect of substance abuse on this study, and consequently that our findings may not generalize to 'healthy' individuals, but we believe that this effect would be small.

In contrast to the few and partly inconsistent findings of studies with healthy subjects, many patient studies have replicated associations between personality traits, mood indicators or neuropsychological test results and DAT or SERT availability. For example, several studies found a lowered midbrain SERT concentration in depressed patients (Newberg *et al*. 2005; Parsey *et al*. 2006; Joensuu *et al*. 2007). In addition, it was demonstrated that psychotherapy could enhance SERT availability (Lehto *et al*. 2008*a*), but to differentiate between subtypes of depression, SERT measurements as predictors were not sensitive enough (Lehto *et al*. 2008*b*). Other studies report on dysfunctional impulsivity linked to SERT availability (Tiihonen *et al*. 1997; Lindström *et al*. 2004; Ryding *et al*. 2006). Koch *et al*. (2007) used the BIS and the BDI, as in our study, to investigate impulsivity and depression scores in relation to SERT in the hypothalamus and the midbrain, using [^{123}I]ADAM SPECT. In a small sample of borderline personality patients ($n=8$) and controls ($n=9$), they were able to demonstrate a correlation between impulsivity and SERT binding when looking at the total sample. As in the present study, no association could be found for BDI measures, in either the patient or the control group.

Therefore, it might be thought that it is only the pathological condition that can be validly related to neurotransmitter system levels. However, normal personality traits, or extreme variants of them, are assumed to represent candidates for the role of 'endophenotypes' (Gottesman & Gould, 2003) and there is some evidence for a continuum between normal personality traits, personality disorders and psychiatric illness. Consequently, personality disorders may represent extremes of normal personality traits. Mental illnesses, in turn, may be extreme variants of

personality disorders. The results from the studies that did not include people with mental illnesses or extreme variants so far have shown only incidental and mainly inconsistent associations between personality traits and neuropsychological functioning and neurotransmitter system levels. Based on our results, we conclude that only in the case of pathological situations do underlying neurotransmitter systems seem to have a predictive value with respect to personality traits and neuropsychological functioning. In the case of normally functioning systems it is not yet possible to link the level of DAT or SERT expression directly to the level of behavior with the current techniques. In conclusion, the present study shows that predictions about behavioral data such as neuropsychological and personality measurements in young healthy people cannot be based on subcortical SERT or striatal DAT availabilities in the brain.

Note

Supplementary material accompanies this paper on the Journal's website (http://journals.cambridge.org/psm).

Declaration of Interest

None.

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