Psychopharmacology (2011) 213:573–581
DOI 10.1007/s00213-010-1926-4

ORIGINAL INVESTIGATION

Cognitive function is related to fronto-striatal serotonin transporter levels – a brain PET study in young healthy subjects

Karine Madsen · David Erritzoe · Erik Lykke Mortensen · Anders Gade · Jacob Madsen · William Baaré · Gitte M. Knudsen · Steen G. Hasselbalch

Received: 30 March 2010 / Accepted: 17 June 2010 / Published online: 10 July 2010

Abstract
Rationale Pharmacological manipulation of serotonergic neurotransmission in healthy volunteers impacts on cognitive test performance. Specifically, markers of serotonin function are associated with attention and executive functioning, long-term memory, and general cognitive ability. The serotonin transporter (SERT) protein is a key regulator in the serotonin system. We hypothesized that higher performance on tests sensitive to serotonin would be associated with higher SERT levels in specific fronto-striatal brain regions.
Methods Thirty-two healthy subjects (25 males, mean age 26.0 years, range 19–37) underwent positron emission tomography using the SERT ligand [^{11}C]DASB. Subjects underwent the following tests: Stroop Color Word Test, Trail Making Test B, Rey's Auditory Verbal Learning Test and Complex Figure Test, logical reasoning subtest from Intelligenz-Struktur-Test 2000 R, and a Danish version of National Adult Reading Test.
Results We found positive associations between performance on the Stroop Color Word Test and right-sided dorsolateral prefrontal SERT binding (R^2=0.12, p=0.048). Furthermore, scores of logical reasoning (correlating with IQ) and educational level associated positively with SERT binding in the caudate, most prominent on the left side (logical reasoning: R^2=0.34, p=0.0026 (left), R^2=0.2, p=0.022 (right), educational level: R^2=0.19, p=0.012 (left), R^2=0.15, p=0.027 (right)). Scores of logical reasoning also associated with left-sided ventrolateral prefrontal cortex (R^2=0.24, p=0.014). There were no significant associations between SERT binding and tests of long-term episodic memory.
Conclusions The results imply that in healthy subjects, high SERT binding in fronto-striatal regions is associated with better performance on tasks involving executive function and logical reasoning.

Keywords Cognition · Intelligence · Executive function · PET · 5-HTT · Serotonin transporter

K. Madsen · D. Erritzoe · G. M. Knudsen · S. G. Hasselbalch
Neurobiology Research Unit, The Neuroscience Centre, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

K. Madsen · D. Erritzoe · E. L. Mortensen · A. Gade · W. Baaré · G. M. Knudsen · S. G. Hasselbalch
Center for Integrated Molecular Brain Imaging, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

J. Madsen
PET and Cyclotron Unit, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

S. G. Hasselbalch
The Memory Clinic, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark

E. L. Mortensen
Institute of Public Health, University of Copenhagen, Copenhagen, Denmark

A. Gade
Institute of Psychology, University of Copenhagen, Copenhagen, Denmark

W. Baaré
Danish Research Center for Magnetic Resonance, Copenhagen University Hospital, Hvidovre, Copenhagen, Denmark

S. G. Hasselbalch (✉)
Neurobiology Research Unit N9201, University Hospital Rigshospitalet, Blegdamsvej 9, 2100 Copenhagen, Denmark
e-mail: sgh@nru.dk

Introduction

Serotonergic disturbances are linked to several neuropsychiatric disorders that involve cognitive dysfunction including depression, bipolar disorder, schizophrenia, and Alzheimer's disease. Serotonergic neurotransmission is involved in many different behaviors such as sleep, mood, aggression, neuroticism, and impulsivity (Siever 2008), but manipulation of serotonergic neurotransmission also impacts on cognitive test performance in healthy volunteers. Cognitive functions sensitive to either lowering of the central serotonergic activity by acute tryptophan depletion (ATD) or, conversely, to stimulation of the serotonergic system by administration of selective reuptake inhibitors (SSRIs) are primarily within the domains of attention, long-term memory (LTM), and cognitive flexibility (for review, see Schmitt et al. 2006).

Most studies have shown that ATD partially impairs LTM (Harrison et al. 2004; McAllister-Williams et al. 2002; Rubinsztein et al. 2001; Schmitt et al. 2000; Riedel et al. 1999), but not all (Hughes et al. 2003; Shansis et al. 2000). Conversely for attention, ATD has in some studies (Booij et al. 2005; Schmitt et al. 2000) although not in all (Gallagher et al. 2003; Sobczak et al. 2002) been reported to improve performance in the Stroop Color Word Test (Jensen and Rohwer 1966), a test that relies heavily on focused attention. In line, serotonergic stimulation with SSRIs reduces sustained attention (Ramaekers et al. 1995; O'Hanlon et al. 1998; Schmitt et al. 2002). These pharmacological manipulations of the serotonergic system are generally unspecific and affect many of the subtypes of pre- and postsynaptic serotonin receptors as well as the serotonin transporter (SERT), although in vivo studies using [^{11}C]DASB binding after ATD have failed to find significant changes in SERT binding (Praschak-Rieder et al. 2005; Milak et al. 2005). Other factors such as low mood and nausea may affect cognition during pharmacological challenges. Alternative strategies for elucidating the role of serotonin in cognition include investigating how cognitive test performance is influenced by genetic polymorphisms of the serotonin system or related to specific elements of the brain serotonin system as measured in imaging studies, e.g., with positron emission tomography (PET).

The SERT protein is a key regulator in the serotonin system, and the highest levels are found in the raphe nuclei and subcortical structures, followed by the hippocampus and the prefrontal cortex (Gurevich and Joyce 1996). SERT controls reuptake of serotonin from the synaptic cleft to the presynaptic neuron, and thereby signal transmission via the postsynaptic serotonin receptors. SERT is encoded by the SLC6A4 gene. Variants within this gene have been associated with specific cognitive capabilities. Subjects homozygous for the functional VNTR2 low expression polymorphisms within the SCLC6A4 gene (an intron two 16 or 17 bp variable number tandem repeat) have been shown to have a faster decline of especially fluid intelligence, semantic memory, and general cognitive ability with age (Payton et al. 2005). Moreover, a positive association between verbal memory scores and SERT binding in the dorsolateral prefrontal cortex (DLPFC) and parietal cortex was observed in the control group of a PET study of SERT binding in MDMA users (McCann et al. 2008). Thus, so far, only limited evidence exists to suggest that an optimal cognitive function requires the presence of a flexible serotonergic neurotransmission, although some lines of evidence point to serotonin as a mediator of cognitive ability throughout life. In order to further link the serotonin system to individual differences in cognition in young healthy subjects, we studied the association between cognition and presynaptic serotonergic function, measured by PET with the specific SERT binding radiotracer [^{11}C]DASB. We addressed the following questions: is SERT correlated to general aspects of cognition, including intelligence and educational levels, and/or is SERT correlated with specific cognitive functions, namely LTM and executive functions involving focused attention and inhibition, as suggested in the literature. In order to answer these questions, we included relevant brain regions in the analysis for each cognitive test in order to avoid multiple comparisons. In these regions, we hypothesized that we would find a positive association between SERT binding and cognitive performance, as a highly dynamic serotonin system was considered important for cognition.

Materials and methods

Subjects

Thirty-two healthy subjects (25 males, mean age 26.0 years (range 19–37)) were recruited through newspaper advertisements. In order to avoid adverse effects of aging on the cognitive test results, only subjects younger than 38 years were included. Written informed consent was obtained according to the Declaration of Helsinki II, and the study was approved by the Copenhagen Region Ethics Committee ((KF) 01-124/04, (KF) 01-156/04, and (KF) 01 2006-20, with amendments). Exclusion criteria included significant medical history, drug or alcohol abuse, psychiatric disorders, or head trauma. Nine subjects were smokers, and none had been exposed to potential neurotoxic drugs of abuse. All subjects had a normal neurological examination and had unremarkable brain magnetic resonance imaging (MRI) scans. A subset of the cohort has been reported earlier in a study on the

association between the personality trait openness and cerebral SERT levels (Kalbitzer et al. 2009). All subjects were scanned during 2006 and 2007. Blood samples were drawn in all subjects to measure the short and long alleles of the 5-HTTLPR polymorphism of the SLC6A4 gene (*S-allele* and *L-allele)*.

Cognitive testing

Cognitive testing was done at a separate day from the day of the PET scan with a median time interval of 56 days (range 1–181). To assess the executive function involving focused attention and inhibition, we administered The Stroop Color Word Test (time score of the incongruent version, errors were not included in analysis), which is a classical test of focused attention (Jensen and Rohwer 1966), and the Trail Making Test B (TMT B; time score), which measures motor and visual speed as well as set switching.

Rey Complex Figure Test and Rey Auditory Learning Test (RAVLT; Rey 1964) delayed scores (after 3 and 20 min, respectively) were chosen for studying episodic visual and verbal LTM.

Intelligence was measured in a subset of 24 subjects at the day of the PET scan with tests of logical reasoning from the German "Intelligenz-Struktur-Test 2000 R" (IST-2000-R; Amthauer 2001; Neubauer et al. 2005). We included the Number Series and Verbal Analogies subtests, as test performances correlate with intelligence quotient (IQ; Amthauer 2001; Neubauer et al. 2005). For each of the two subtests, subjects were given 10 min to solve as many as they could of 20 tasks. Additionally, the Danish Adult Reading Test 45 (DART45), which is a 45-word Danish version of the National Adult Reading Test (Nelson and O'Connell 1978) was administered to all subjects. This test correlates substantially with verbal IQ, but primarily reflects knowledge of pronunciation of irregular words acquired throughout life.

Educational level was evaluated by adding number of school years in primary school to upper secondary level (9–12 in all) with a score (1–5) reflecting level of vocational training or degree.

MRI

Magnetic resonance imaging was conducted on a Siemens Magnetom Trio 3T MR scanner. High-resolution 3D T1-weighted (matrix 256×256; 1×1×1 mm voxels) and 2D T2-weighted sequences were acquired. The T1-weighted brain MR images were segmented into gray matter, white matter, and cerebrospinal fluid using Statistical Parametric Mapping (SPM2; Wellcome Department of Cognitive Neurology, London, UK). This enabled extraction of the PET Volume of Interest (VOI) signal from gray matter voxels only.

Regions of interest

In order to avoid multiple comparisons, we restricted our analyses by choosing relevant brain regions to be included in the analysis for each cognitive test:

> The lateral prefrontal cortex (LPFC) was the primary target in the analysis of executive functions. Neuroimaging activation studies have suggested that the ventral part of the LPFC (VLPFC) is recruited during tasks that require the selection of specific item information, whereas the DLPFC is additionally activated during tasks that require organizational processing. The right DLPFC and the anterior cingulate gyrus (ACC) were the primary targets for the association with The Stroop Color Word Test, as these are the most commonly activated regions in fMRI studies of Stroop interference tasks (Harrison et al. 2005; Haupt et al. 2009; Hyafil et al. 2009).
>
> Hippocampus and LPFC were the primary targets for associations with LTM. In addition to the well-established hippocampal activation in memory formation (Cabeza and Nyberg 2000), the involvement of LPFC in organizational LTM has been documented both in neuropsychological studies (including patients with focal LPFC lesions) and in neuroimaging studies (for review, see (Blumenfeld and Ranganath 2007)). Due to hemispheric lateralization, we correlated verbal LTM (Rey's Auditory Verbal Learning Test, delayed recall) with left hippocampus and left LPFC, and visual LTM (Rey's Complex Figure delayed recall) with right hippocampus and right LPFC.
>
> For intelligence and educational levels, the choice of fronto-striatal regions were the primary target in the analyses as the LPFC may exert its control of executive functions and thereby affect intelligence through its connections with subcortical and posterior brain regions, as reviewed by Jurado and Rosselli (Jurado and Rosselli 2007). In line, larger cortical gray matter thickness and less white matter have been associated with higher intelligence, particularly in the prefrontal and posterior temporal cortices (Narr et al. 2007).

The selected regions (caudate, putamen, VLPFC (including Brodmann areas 44, 45 and 47), DLPFC (including Brodmann areas 9 and 46), hippocampus, and anterior cingulate gyrus) were automatically delineated on each subject's MRI in a user-independent fashion with the Pvelab software package as described by (Svarer et al. 2005; freely available on www.nru.dk/downloads). Gray matter volumes of included regions are listed in Table 2.

PET imaging and quantification of SERT binding

PET scans were performed with an 18-ring GE-Advance scanner (General Electric, Milwaukee, WI, USA), operating in 3D acquisition mode producing 35 image slices with an inter slice distance of 4.25 mm. The total axial field of view was 15.2 cm. with an approximate in-plane resolution of 6 mm.

A 90-min dynamic scan was started immediately after bolus injection of mean 479.2 (range 279–601) MBq [^{11}C]DASB. The scan acquisition consisted of 36 time frames, increasing progressively in duration from 10 s to 10 min. After acquisition, attenuation- and decay-corrected recordings were reconstructed by filtered back projection using a 6 mm Hann filter. Frames 10-36 were aligned using AIR 5.2.5 (Woods et al. 1992) to correct for movements during scan.

The [^{11}C]DASB PET image was co-registered to the MRI using the AIR algorithm (Woods et al. 1992). The quality of each co-registration was evaluated by visual inspection in three planes.

The kinetic modeling was performed using the PMOD software version 2.9, build 2 (PMOD Technologies). Time-activity curves were extracted from gray matter voxels in VOIs only. The binding potential of specific tracer binding (BP_{ND}) was calculated using the Ichise Multi-linear Reference Tissue Method 2 with cerebellum (excluding vermis) as a reference region representing non-specific binding only (Ichise et al. 2003). The k2′ (clearance rate constant from cerebellum) was fixed by applying MRTM on time-activity curve data from a high-binding region composed from volume-weighted average of thalamus, putamen, and caudate (Ichise et al. 2003).

Statistics

The primary outcome, i.e., the effect of regional SERT binding on cognitive performance, was modeled in SAS 9.1 (SAS Institute Inc.) using a linear regression analysis for each cognitive test with performance as the dependent variable. Age was included in the model as an explanatory covariate when significant (p value<0.05), since cognitive performance in some tests may change with age and vivo imaging studies have shown a decline in SERT binding in with aging, albeit in cohorts with larger age span and in varying regions (Meyer et al. 2001; Reimold et al. 2008; Kalbitzer et al. 2009).

Associations between individual performances in tests and IQ (measured by the IST-2000-R subtest) and between performance in tests within the same cognitive domain were tested in a linear regression model.

Influence of 5-HTTLPR polymorphism and smoking habits on cognitive function, SERT binding, and gray matter volume was analyzed with t tests.

Table 1 Demographic data and cognitive test scores

	Mean ± SD
Sex	25 M/7F
Age (years)	26.0±5.1
BMI (kg/m^2)	25.4±5.4
Education (score 9–17)	15.6±1.9
RAVLT (score)	12.1±2.2
Rey's Complex Figure (score)	25.0±6.6
Trail Making B (s)	52.9±13.7
Stroop incongruity (s)	109.2±31.2
DART45 (score)	28.3±7.4
IST-2000-R (score) N=24	22.1±8.0

A significance level of p<0.05 was adopted throughout the analyses, without correction for multiple comparisons.

Results

All 32 individuals completed the cognitive testing, and 24 individuals performed the IST-2000-R subtest. Table 1 shows demographic data and test scores for the subjects. The measured regional [^{11}C]DASB BP_{ND} values and gray matter volumes are listed in Table 2. The previously established regional variation in SERT binding (Gurevich and Joyce 1996) was corroborated in our study (order of binding: striatum>hippocampus>anterior cingulate cortex> prefrontal cortex). We found a decrease with aging in cognitive performance in TMT B (R^2=0.12, estimate= 0.95 s/year±0.46, p=0.047), and a tendency to an increase in DART45 with aging (R^2=0.11, estimate=0.47/year±0.25,

Table 2 Regional SERT binding levels measured as BP_{ND} of [^{11}C] DASB and gray matter volumes

Region	BP_{ND} Mean ± SD	Gray matter volume (ml) Mean ± SD
Left putamen	1.65±0.19	3.62±0.38
Right putamen	1.64±0.17	3.50±0.42
Left caudate	1.44± 0.23	2.40±0.30
Right caudate	1.44±0.25	2.22±0.28
Left VLPFC	0.26±0.05	6.45±0.71
Right VLPFC	0.24±0.05	6.31±0.80
Left DLPFC	0.19±0.07	9.43±0.85
Right DLPFC	0.21±0.06	9.66±0.97
Left hippocampus	0.68±0.10	2.92±0.23
Right hippocampus	0.63±0.11	2.78±0.23
Left ACC	0.47±0.07	3.75±0.41
Right ACC	0.49±0.06	3.34±0.36

p=0.067). Otherwise aging had no effect on cognitive performance in this cohort.

We found a tendency to a positive association between IQ (measured by the IST-2000-R subtest) and performance in TMT B (p=0.06, corrected for age) and RAVLT (p=0.06), but no association was found to Stroop Color Word Test or Rey Complex Figure Test.

Smokers had lower gray matter volume (p=0.03) and SERT binding (p=0.05) in the left hippocampus, they also had lower DART45 score (p=0.04). No other differences between smokers and no-smokers were found.

Executive function

There was a significant association between performance in the Stroop Color Word Test and SERT binding in the right DLPFC (R^2=0.12, estimate=−174 s/BP_{ND}±84, p=0.048) with faster performance associating with higher SERT binding (Fig. 1). No associations were found between Stroop performance and SERT binding in the ACC. However, post hoc analysis of fronto-striatal ROIs showed tendencies in the same direction in left VLPFC (R^2=0.08, estimate=−205 s/BP_{ND}±114, p=0.082), the right caudate (R^2=0.09, estimate=−38 s/BP_{ND}±22, p=0.088) and the left DLPFC (R^2=0.08, estimate=−139 s/BP_{ND}±84, p=0.11).

No significant associations were found between regional SERT binding in LPFC and the performance in the TMT B, and only a tendency to an association between individual performance in TMT B and Stroop Color Word Test (p=0.085) was found.

Long-term memory

There was no association between regional SERT binding and performance in RAVLT or Rey Complex Figure Test, neither in hippocampus nor in LPFC ROIs. Further, we did not find any significant association between the individuals' performance in the two tests for episodic verbal and visual memory (p=0.75).

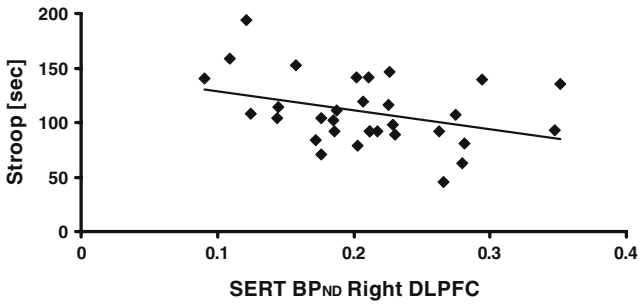

Fig. 1 The association between performance speed in Stroop Color Word Test incongruent version and SERT binding in the DLPFC region shows a positive correlation between performance and SERT binding

Table 3 Results of linear regression analysis with performance in IST-2000-R as dependent variable of the regional SERT binding

	Estimate ± SE	P value	R^2
Left caudate	18.35±5.41/BP_{ND}	0.0026	0.34
Right caudate	13.21±5.36/BP_{ND}	0.022	0.22
Left VLPFC	75.73±28.34/BP_{ND}	0.014	0.24
Right VLPFC	34.12±29.27/BP_{ND}	0.25	0.06
Left DLPFC	41.92±22.71/BP_{ND}	0.078	0.13
Right DLPFC	32.91±23.85/BP_{ND}	0.18	0.08
Left putamen	12.25±8.36/BP_{ND}	0.16	0.09
Right putamen	9.03±9.46/BP_{ND}	0.35	0.04

Intelligence and education

There were positive associations between the IST-2000-R subtest scores and fronto-striatal SERT binding (see Table 3) with the strongest associations in the left hemisphere: caudate (p=0.0026, Fig. 2), VLPFC (p=0.014), and a tendency in DLPFC (p=0.078). In the right hemisphere, a positive association was found only for the caudate (p=0.041).

Performance in DART45 did not associate with fronto-striatal SERT binding; only a trend towards a positive association was found between SERT binding in the left caudate and DART45 (R^2=0.10, estimate=9.81 score/BP_{ND}±5.44, p=0.082, adjusted for age). However, performance on the two tests for intelligence associated (p=0.041), and outcomes from both tests also associated with educational levels (IST-2000-R: p=0.002, DART45: p=0.005).

A positive association was found between educational level and SERT binding in the caudate—again with the strongest association in the left hemisphere, see Fig. 3 (left caudate, R^2=0.19; estimate=3.68 score/BP_{ND}±1.38, p=0.012. Right caudate, R^2=0.15; estimate=3.01 score/BP_{ND}±1.29, p=0.027).

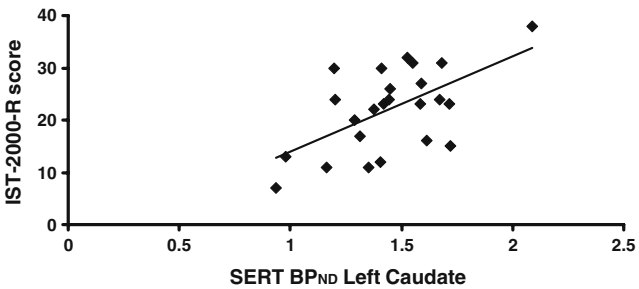

Fig. 2 The positive association between the IST-2000-R intelligence score and regional SERT binding is here illustrated for the left caudate

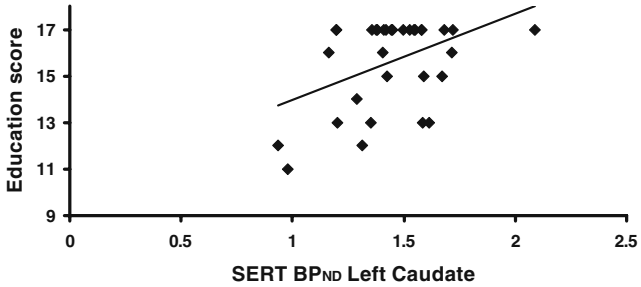

Fig. 3 Illustration of the positive association between educational level and SERT binding in the left caudate

Gene effects

Thirteen test persons were homozygote *L-allele* carriers, six were homozygote *S-allele* carriers, and ten were heterozygote. For three subjects, genomic DNA was not successfully purified. No differences in performance in the cognitive tests were found between carriers of the different alleles of the 5-HTTLPR polymorphism. Homozygote *S-allele* carriers had lower SERT binding compared to heterozygotes and homozygote *L-allele* carriers in the left DLPFC (p=0.04), right DLPFC (p=0.03), and right caudate (p=0.04); further, they had reduced hippocampus volume (left, p=0.01; right, p=0.04).

Discussion

In young healthy adults, we identified positive associations between intelligence scores and SERT binding in the caudate nucleus and left-sided VLPFC, and between educational level and SERT binding in the left caudate nucleus. We also found positive associations between executive function and right-sided dorsolateral prefrontal cortical SERT binding. We were not, however, able to demonstrate any association between LTM and SERT binding. Our data suggest that high fronto-striatal SERT binding is predictive of a better performance on tasks involving executive function and logical reasoning. There were no associations between cognitive performance in any of the tasks and the regional gray matter volume or genotype. Smoking was negatively associated to performance only on DART45, this association may be influenced by socio-economic confounders, and was not used as a co-variate in the analysis.

Our results imply that high fronto-striatal SERT binding have beneficial effects on some cognitive functions. The inter-individual variation in SERT binding can be interpreted as a surrogate marker of variation in the number of SERT molecules primarily located at the pre-synaptic neuron. Thus, we suggest that in healthy subjects, high fronto-striatal levels of SERT may correspond to an efficient 5-HT reuptake system, being able to rapidly change and adjust extracellular serotonin concentration in the brain.

The inter-individual variation in SERT binding could alternatively result from variation in the number of serotonergic neurons, which have their soma in the raphe nuclei in the midbrain. However, a post hoc analysis showed no associations between SERT binding in the raphe region (BP_{ND} 3.60 (0.48)) and performance on neither the Stroop Color Word Test, the IST-2000-R subtest or educational level, suggesting that the significant associations are not explained by the number of serotonergic neurons in the raphe region.

In contrast to our findings, no associations were found between cognitive performance and the 5-HT_{1A} receptor in a PET study of healthy subjects (Borg et al. 2006), suggesting that the reuptake system is better related to cognitive function than the 5-HT_{1A} receptor.

Executive function

The positive association between speed performance on the Stroop Color Word Test and SERT binding in the right DLPFC may reflect that a high SERT level enables the individual to quickly adapt the serotonergic tone to increasing attentional demands by reducing the amount of endogenous serotonin in the synaptic cleft, in correspondence with a generally improved attention following ATD (Schmitt et al. 2000; Booij et al. 2005). This effect may be mediated through lower serotonergic tone on other neurotransmitter systems involved in the ACC-DLPFC circuit (i.e., dopaminergic and glutamatergic systems (Boulougouris and Tsaltas 2008)). Yet, on the other hand, administration of SSRIs does not impair focused attention (Schmitt et al. 2002; Hindmarch and Bhatti 1988; Wingen et al. 2007). Decreased activity in fMRI within right DLPFC and ACC during discrimination tasks has been found in adolescents with attention-deficit hyperactivity disorder (Smith et al. 2008) as well as in adolescents with major depressive disorder (Halari et al. 2009). We did, however, only find an association to SERT binding in the right DLPFC and not in ACC.

A study from our group in 50 healthy subjects showed a negative association between SERT binding measured with [^{11}C]DASB and the personality trait openness (Kalbitzer et al. 2009), and it seems reasonable that focused attention and openness may be negatively associated.

Genetic studies have associated attention and other executive functions to the short 5-HTTLPR allele of the SLC6A4 gene (Strobel et al. 2007; Borg et al. 2009; Roiser et al. 2007), but we did not find gene effects in this relatively small sample for such associations. However, differences in SERT binding between short and long

5-HTTLPR allele carriers have only been described in few studies and in different regions (Kalbitzer et al. 2009; Praschak-Rieder et al. 2007; Reimold et al. 2007) which is in accordance with our results.

No significant associations were found between regional fronto-strialtal SERT binding and the speed performance in the TMT B. However, individual differences in TMT B in this young and well-educated cohort may be more related to the visuomotor speed requirements of the test than set shifting, which is supported by the decrease in performance with age and the lack of association between individual performance in TMT B and Stroop Color Word Test.

Long-term memory

Our study showed no associations between LTM test scores and SERT binding in the fronto-striatal regions or in the hippocampus. However, Rey Complex Figure Test and Rey Auditory Learning Test are primarily developed to examine patients with cognitive problems and the people enrolled in the present study were relatively well educated (see Table 1) and there was no association between the individual's performances in the two tests. In addition, previous studies have shown that impairment of episodic LTM in healthy volunteers after ATD was most pronounced with a delay in recall for more than 30 min (Riedel et al. 1999). In this study, the delays for recall were only 3 and 20 min in Rey Complex Figure Test and RAVLT, respectively, and an association between SERT levels and delayed recall for more than 30 min cannot be excluded.

Intelligence and education

The positive association between IST-2000-R performance and SERT binding was stronger in the left hemisphere. This was to be expected, as the applied test is composed of tasks for logical reasoning (Verbal Analogies and Number Series), which primarily is associated with the left hemisphere (Reverberi et al. 2009). Other factors of intelligence that primarily are associated with the right hemisphere include spatial or geometric tasks, but these tasks were not explored in the present study. We found that the level of SERT binding in the left caudate explained 34% of the variance in IST-2000-R scores. It could be hypothesized that this association between intelligence and SERT binding in fronto-striatal regions reflect the same underlying modulation of cognition by serotonin as described above for the association between prefrontal SERT binding and attentional aspects of cognition.

Even though performance on the two tests (IST-2000-R and DART45) is associated, the association to SERT binding was not found for the DART45. This discrepancy may be related to the very different requirements of the tests. DART45 requires the pronunciation of irregular words and is a test of "crystallized intelligence", while the IST-2000-R subtests for logical reasoning are related to "fluid intelligence". Even though these two aspects of intelligence are correlated, and both tests associate with educational level, they are not identical. DART45 is also a test of learned abilities and as expected, a tendency to an increase with aging was found, even in this relatively young cohort. Further, DART45 might be more influenced by the generally high education level of the cohort.

Conclusions

In conclusion, in the present study, we found further evidence for the notion that the serotonergic system is of importance for cognitive function in young healthy subjects. We found a positive association between regional SERT binding and cognitive performance, suggesting that an efficient 5-HT reuptake system contributes to better performance in certain cognitive tasks. Thus, we found positive associations between executive function and right-sided dorsolateral prefrontal cortical SERT binding. Furthermore, scores of intelligence associated positively with SERT binding in the caudate and left-sided ventrolateral prefrontal cortex and educational level with SERT binding in the left caudate. The results imply that high SERT binding in fronto-striatal regions is related to better performance on tasks involving executive function and logical reasoning, but a corroboration of our results in a larger sample would be required before firm conclusions can be drawn.

Acknowledgments Supported by The Lundbeck Foundation, Rigshospitalet, and the Danish Medical Research Council. The John and Birthe Meyer Foundation is gratefully acknowledged for the donation of the Cyclotron and PET scanner.

Disclosure/conflicts of interest The authors declare that, except for income received from their primary employers, no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interest.

References

Amthauer R, Brocke B, Liepmann D, Beauducel A (2001) Intelligenz-Struktur-Test 2000, R. Göttingen, Hogrefe

Blumenfeld RS, Ranganath C (2007) Prefrontal cortex and long-term memory encoding: an integrative review of findings from neuropsychology and neuroimaging. Neuroscientist 13:280–291

Booij L, Van der Does AJ, Haffmans PM, Riedel WJ, Fekkes D, Blom MJ (2005) The effects of high-dose and low-dose tryptophan depletion on mood and cognitive functions of remitted depressed patients. J Psychopharmacol 19:267–275

Borg J, Andrée B, Lundberg J, Halldin C, Farde L (2006) Search for correlations between serotonin 5-HT1A receptor expression and cognitive functions—a strategy in translational psychopharmacology. Psychopharmacology (Berl) 185:389–394

Borg J, Henningsson S, Saijo T, Inoue M, Bah J, Westberg L, Lundberg J, Jovanovic H, Andrée B, Nordstrom AL, Halldin C, Eriksson E, Farde L (2009) Serotonin transporter genotype is associated with cognitive performance but not regional 5-HT1A receptor binding in humans. Int J Neuropsychopharmacol 12:783–792

Boulougouris V, Tsaltas E (2008) Serotonergic and dopaminergic modulation of attentional processes. Prog Brain Res 172:517–542

Cabeza R, Nyberg L (2000) Imaging cognition II: an empirical review of 275 PET and fMRI studies. J Cogn Neurosci 12:1–47

Gallagher P, Massey AE, Young AH, McAllister-Williams RH (2003) Effects of acute tryptophan depletion on executive function in healthy male volunteers. BMC Psychiatry 3:10

Gurevich EV, Joyce JN (1996) Comparison of [3H]paroxetine and [3H]cyanoimipramine for quantitative measurement of serotonin transporter sites in human brain. Neuropsychopharmacology 14:309–323

Halari R, Simic M, Pariante CM, Papadopoulos A, Cleare A, Brammer M, Fombonne E, Rubia K (2009) Reduced activation in lateral prefrontal cortex and anterior cingulate during attention and cognitive control functions in medication-naïve adolescents with depression compared to controls. J Child Psychol Psychiatry 50:307–316

Harrison BJ, Olver JS, Norman TR, Burrows GD, Wesnes KA, Nathan PJ (2004) Selective effects of acute serotonin and catecholamine depletion on memory in healthy women. J Psychopharmacol 18:32–40

Harrison BJ, Shaw M, Yücel M, Purcell R, Brewer WJ, Strother SC, Egan GF, Olver JS, Nathan PJ, Pantelis C (2005) Functional connectivity during Stroop task performance. Neuroimage 24:181–191

Haupt S, Axmacher N, Cohen MX, Elger CE, Fell J (2009) Activation of the caudal anterior cingulate cortex due to task-related interference in an auditory Stroop paradigm. Hum Brain Mapp Sep 30(9):3043–56

Hindmarch I, Bhatti JZ (1988) Psychopharmacological effects of sertraline in normal, healthy volunteers. Eur J Clin Pharmacol 35:221–223

Hughes JH, Gallagher P, Stewart ME, Matthews D, Kelly TP, Young AH (2003) The effects of acute tryptophan depletion on neuropsychological function. J Psychopharmacol 17:300–309

Hyafil A, Summerfield C, Koechlin E (2009) Two mechanisms for task switching in the prefrontal cortex. J Neurosci 29:5135–5142

Ichise M, Liow JS, Lu JQ, Takano A, Model K, Toyama H, Suhara T, Suzuki K, Innis RB, Carson RE (2003) Linearized reference tissue parametric imaging methods: application to [11C]DASB positron emission tomography studies of the serotonin transporter in human brain. J Cereb Blood Flow Metab 23:1096–1112

Jensen AR, Rohwer WD (1966) The Stroop Color-Word Test: a review. Acta Psychol (Amst) 25:36–93

Jurado MB, Rosselli M (2007) The elusive nature of executive functions: a review of our current understanding. Neuropsychol Rev 17:213–233

Kalbitzer J, Frokjaer VG, Erritzoe D, Svarer C, Cumming P, Nielsen FA, Hashemi SH, Baaré WF, Madsen J, Hasselbalch SG, Kringelbach ML, Mortensen EL, Knudsen GM (2009) The personality trait openness is related to cerebral 5-HTT levels. Neuroimage 45:280–285

McAllister-Williams RH, Massey AE, Rugg MD (2002) Effects of tryptophan depletion on brain potential correlates of episodic memory retrieval. Psychopharmacology (Berl) 160:434–442

McCann UD, Szabo Z, Vranesic M, Palermo M, Mathews WB, Ravert HT, Dannals RF, Ricaurte GA (2008) Positron emission tomographic studies of brain dopamine and serotonin transporters in abstinent (+/−)3, 4-methylenedioxymethamphetamine ("ecstasy") users: relationship to cognitive performance. Psychopharmacology (Berl) 200:439–450

Meyer JH, Wilson AA, Ginovart N, Goulding V, Hussey D, Hood K, Houle S (2001) Occupancy of serotonin transporters by paroxetine and citalopram during treatment of depression: a [(11)C] DASB PET imaging study. Am J Psychiatry 158:1843–1849

Milak MS, Ogden RT, Vinocur DN, Van Heertum RL, Cooper TB, Mann JJ, Parsey RV (2005) Effects of tryptophan depletion on the binding of [11C]-DASB to the serotonin transporter in baboons: response to acute serotonin deficiency. Biol Psychiatry 57:102–106

Narr KL, Woods RP, Thompson PM, Szeszko P, Robinson D, Dimtcheva T, Gurbani M, Toga AW, Bilder RM (2007) Relationships between IQ and regional cortical grey matter thickness in healthy adults. Cereb Cortex 17:2163–2171

Nelson HE, O'Connell A (1978) Dementia: the estimation of premorbid intelligence levels using the New Adult Reading Test. Cortex 14:234–244

Neubauer AC, Grabner RH, Fink A, Neuper C (2005) Intelligence and neural efficiency: further evidence of the influence of task content and sex on the brain-IQ relationship. Brain Res Cogn Brain Res 25:217–225

O'Hanlon JF, Robbe HW, Vermeeren A, van Leeuwen C, Danjou PE (1998) Venlafaxine's effects on healthy volunteers' driving, psychomotor, and vigilance performance during 15-day fixed and incremental dosing regimens. J Clin Psychopharmacol 18:212–221

Payton A, Gibbons L, Davidson Y, Ollier W, Rabbitt P, Worthington J, Pickles A, Pendleton N, Horan M (2005) Influence of serotonin transporter gene polymorphisms on cognitive decline and cognitive abilities in a nondemented elderly population. Mol Psychiatry 10:1133–1139

Praschak-Rieder N, Wilson AA, Hussey D, Carella A, Wei C, Ginovart N, Schwarz MJ, Zach J, Houle S, Meyer JH (2005) Effects of tryptophan depletion on the serotonin transporter in healthy humans. Biol Psychiatry 58:825–830

Praschak-Rieder N, Kennedy J, Wilson AA, Hussey D, Boovariwala A, Willeit M, Ginovart N, Tharmalingam S, Masellis M, Houle S, Meyer JH (2007) Novel 5-HTTLPR allele associates with higher serotonin transporter binding in putamen: a [(11)C] DASB positron emission tomography study. Biol Psychiatry 62:327–331

Ramaekers JG, Muntjewerff ND, O'Hanlon JF (1995) A comparative study of acute and subchronic effects of dothiepin, fluoxetine and placebo on psychomotor and actual driving performance. Br J Clin Pharmacol 39:397–404

Reimold M, Smolka MN, Schumann G, Zimmer A, Wrase J, Mann K, Hu XZ, Goldman D, Reischl G, Solbach C, Machulla HJ, Bares R, Heinz A (2007) Midbrain serotonin transporter binding potential measured with [11C]DASB is affected by serotonin transporter genotype. J Neural Transm 114:635–639

Reimold M, Batra A, Knobel A, Smolka MN, Zimmer A, Mann K, Solbach C, Reischl G, Schwärzler F, Gründer G, Machulla HJ, Bares R, Heinz A (2008) Anxiety is associated with reduced central serotonin transporter availability in unmedicated patients with unipolar major depression: a [11C]DASB PET study. Mol Psychiatry 13(606– 13):557

Reverberi C, Shallice T, D'Agostini S, Skrap M, Bonatti LL (2009) Cortical bases of elementary deductive reasoning: inference, memory, and metadeduction. Neuropsychologia 47:1107–1116

Rey AR (1964) L'examen clinique en psychologie. Presses Universitaires de France, Paris

Riedel WJ, Klaassen T, Deutz NE, van Someren A, van Praag HM (1999) Tryptophan depletion in normal volunteers produces selective impairment in memory consolidation. Psychopharmacology (Berl) 141:362–369

Roiser JP, Müller U, Clark L, Sahakian BJ (2007) The effects of acute tryptophan depletion and serotonin transporter polymorphism on emotional processing in memory and attention. Int J Neuropsychopharmacol 10:449–461

Rubinsztein JS, Rogers RD, Riedel WJ, Mehta MA, Robbins TW, Sahakian BJ (2001) Acute dietary tryptophan depletion impairs maintenance of "affective set" and delayed visual recognition in healthy volunteers. Psychopharmacology (Berl) 154:319–326

Schmitt JA, Jorissen BL, Sobczak S, van Boxtel MP, Hogervorst E, Deutz NE, Riedel WJ (2000) Tryptophan depletion impairs memory consolidation but improves focussed attention in healthy young volunteers. J Psychopharmacol 14:21–29

Schmitt JA, Ramaekers JG, Kruizinga MJ, van Boxtel MP, Vuurman EF, Riedel WJ (2002) Additional dopamine reuptake inhibition attenuates vigilance impairment induced by serotonin reuptake inhibition in man. J Psychopharmacol 16:207–214

Schmitt JA, Wingen M, Ramaekers JG, Evers EA, Riedel WJ (2006) Serotonin and human cognitive performance. Curr Pharm Des 12:2473–2486

Shansis FM, Busnello JV, Quevedo J, Forster L, Young S, Izquierdo I, Kapczinski F (2000) Behavioural effects of acute tryptophan depletion in healthy male volunteers. J Psychopharmacol 14:157–163

Siever LJ (2008) Neurobiology of aggression and violence. Am J Psychiatry 165:429–442

Smith AB, Taylor E, Brammer M, Halari R, Rubia K (2008) Reduced activation in right lateral prefrontal cortex and anterior cingulate gyrus in medication-naïve adolescents with attention deficit hyperactivity disorder during time discrimination. J Child Psychol Psychiatry 49:977–985

Sobczak S, Riedel WJ, Booij I, Aan Het Rot M, Deutz NE, Honig A (2002) Cognition following acute tryptophan depletion: difference between first-degree relatives of bipolar disorder patients and matched healthy control volunteers. Psychol Med 32:503–515

Strobel A, Dreisbach G, Müller J, Goschke T, Brocke B, Lesch KP (2007) Genetic variation of serotonin function and cognitive control. J Cogn Neurosci 19:1923–1931

Svarer C, Madsen K, Hasselbalch SG, Pinborg LH, Haugbøl S, Frøkjaer VG, Holm S, Paulson OB, Knudsen GM (2005) MR-based automatic delineation of volumes of interest in human brain PET images using probability maps. Neuroimage 24:969–979

Wingen M, Kuypers KP, Ramaekers JG (2007) The role of 5-HT1a and 5-HT2a receptors in attention and motor control: a mechanistic study in healthy volunteers. Psychopharmacology (Berl) 190:391–400

Woods RP, Cherry SR, Mazziotta JC (1992) Rapid automated algorithm for aligning and reslicing PET images. J Comput Assist Tomogr 16:620–633