# Altered Interregional Molecular Associations of the Serotonin Transporter in Attention Deficit/ Hyperactivity Disorder Assessed with PET

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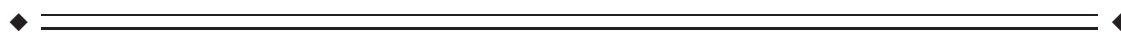
Abstract: Altered serotonergic neurotransmission has been found to cause impulsive and aggressive behavior, as well as increased motor activity, all exemplifying key symptoms of ADHD. The main objectives of this positron emission tomography (PET) study were to investigate the serotonin transporter binding potential (SERT BP_{ND}) in patients with ADHD and to assess associations of SERT BP_{ND} between the brain regions. 25 medication-free patients with ADHD (age ± SD; 32.39 ± 10.15; 10 females) without any psychiatric comorbidity and 25 age and sex matched healthy control subjects (33.74 ± 10.20) were measured once with PET and the highly selective and specific radioligand [^{11}C]DASB. SERT BP_{ND} maps in nine *a priori* defined ROIs exhibiting high SERT binding were compared between groups by means of a linear mixed model. Finally, adopted from structural and functional connectivity analyses, we performed correlational analyses using regional SERT binding potentials to examine molecular interregional associations between all selected ROIs. We observed significant differences in the interregional correlations between the precuneus and the hippocampus in patients with ADHD compared to healthy controls, using SERT BP_{ND} of the investigated ROIs ($P < 0.05$; Bonferroni corrected). When correlating SERT BP_{ND} and age in the ADHD and the healthy control group, we confirmed an age-related decline in brain SERT binding in the thalamus and insula ($R^2 = 0.284$, $R^2 = 0.167$, $Ps < 0.05$; Bonferroni corrected). The results show significantly different interregional molecular associations of the SERT expression for the precuneus with hippocampus in patients with ADHD, indicating presumably altered functional coupling. Altered interregional coupling between brain regions might be a sensitive approach to demonstrate functional and molecular alterations in psychiatric conditions. *Hum Brain Mapp 38:792–802, 2017.*
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Key words: neuroimaging; ADHD; positron emission tomography; PET; serotonin; SERT; interregional molecular associations

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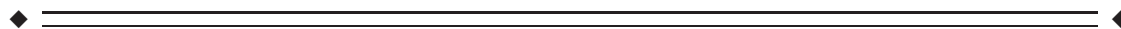
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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is characterized by inappropriate inattention, hyperactivity, impulsive behaviour and emotional dysregulation [American Psychiatric Association, 2013; Rosler et al., 2010], as well as by a certain constellation of deficits in executive functions. ADHD is considered to be the most prevalent neurodevelopmental disorder, prevalance rates are estimated to range between 8% and 12% in childhood [Biederman and Faraone, 2005]. In about 30% of children diagnosed with ADHD [Barbaresi et al., 2013], especially inattentive symptoms persist into adulthood.

Frequently prescribed stimulant and non-stimulant psychopharmacological treatment for patients with ADHD are suggested to unfold efficacy through modulation of dopaminergic (DA) and norepinephrinergic neurotransmission in cortical and subcortical brain circuits and improvement of neurocognitive deficits [Castells et al., 2011; Chamberlain et al., 2009; Retz et al., 2011]. Although the serotoninergic system is not a direct target for ADHD medication, evidence from pharmacological, genetic and animal studies suggest an involvement of the serotonergic neurotransmission in the neurobiological mechanisms of ADHD [for review see (Banerjee and Nandagopal, 2015)].

Although methylphenidate does not inhibit the serotonin transporter, amphetamines enhance serotonergic release [Bymaster et al., 2002; Kuczenski and Segal, 1997]. A recently published positron emission tomography (PET) animal study found that atomoxetine applied at clinical dosage blocks the norepinephrine transporter as well as the serotonin transporter (SERT) [Ding et al., 2014] and atomoxetine has been shown to significantly alleviate symptoms in adult ADHD patients [Adler et al., 2009]. This has led some researchers to suggest that serotonergic transmission might also be of relevant to ADHD treatment and neuropathology [Gainetdinov et al., 1999].

Several lines of evidence suggest that serotonin is involved in impulsive behaviour and extensive motor activity [Dalley and Roiser, 2012; Winstanley et al., 2006]. Serotonergic neurons in the medial and dorsal raphe project into the striatum, ventral tegmental area and nucleus accumbens as well as into the amygdala, hippocampus and the frontal cortex [Muller and Jacobs, 2009]. Serotonin regulates dopaminergic neurotransmission via projections to the dopaminergic neurons in the midbrain and neuronal interactions between these neurotransmitters are found to profoundly modulate impulsive behaviour [Oades, 2008;

Abbreviations

AAL	Automated anatomical labelling
ADHD	Attention deficit hyperactivity disorder
HC	Healthy control subects
PET	Positron emission tomography
SERT	Serotonin Transporter
SPECT	Single photon emission tomography

Wood and Wren, 2008]. Furthermore, a deficit to withhold attention for an adequate time, related to a specific context, can lead to emotional dysregulation, a symptom of ADHD that affects patients markedly throughout lifetime. Brain regions implicated in emotional dysregulation comprise the striatum, amygdala and the medial prefrontal cortex, regions that are strongly modulated by serotonergic neurotransmission [Shaw et al., 2014].

Neuroimaging studies have been demonstrating that patients with ADHD display altered neural activation for inhibition and attention in frontal, parietal and thalamic brain regions as well as in the basal ganglia [Aron and Poldrack, 2005; Hart et al., 2013]. In comparison to healthy control subjects (HC), the administration of fluoxetine, a selective serotonin reuptake inhibitor, prior to functional magnetic resonance imaging (fMRI) measurements, has been shown to normalize neuronal activation during a stop signal task measuring motor inhibition in the orbitofrontal cortex and in the basal ganglia in 18 patients with ADHD [Chantiluke et al., 2015]. Fluoxetine, as well as its metabolite norfluoxetine, also binds to the norepinephrine transporter, although to a far lesser extent [Wong et al., 1993]. In addition, Fluoxetine has been found to be effective to improve attention and alleviate hyperactivity in children with ADHD and non-bipolar comorbid mood-disorders [Barrickman et al., 1991; Quintana et al., 2007].

With a remarkable heritability estimated to be 77% [Faraone et al., 2005], ADHD exemplifies a spectrum disorder with behavioural and personality traits, which underlie a combination and an interaction of genetic and environmental factors [Fliers et al., 2012]. The gene encoding the serotonin transporter (SERT; SLC6A4) as well as the genes encoding certain serotonergic receptors comprise various single nucleotide polymorphisms that have been examined in ADHD and other neuropsychiatric disorders and were found to be influencing the susceptibility to ADHD [Faraone and Khan, 2006; van der Meer et al., 2014]. Thus, the SERT gene is alleged to play a main role in ADHD pathogenesis.

Studies applying PET or single photon emission tomography (SPECT) in adult patients with ADHD have explored glucose, blood flow metabolismand [for review see (Zimmer, 2009)] and especially the dopaminergic and noradrenergic neurotransmitter systems. Dysfunctional dopaminergic signaling, including investigations on the dopamine transporter [Fusar-Poli et al., 2012] and dopamine receptors [del Campo et al., 2013; Volkow et al., 2009], has been identified in different brain regions, though results remain inconsistent. In a recently published PET study, we found no difference in norepinephrine transporter in subcortical regions between patients with ADHD and HC [Vanicek et al., 2014]. A PET study has investigated serotonin transporter binding potential (SERT BP_{ND}) in patients with ADHD [Karlsson et al., 2013], using [^{11}C]MADAM, which is a frequently used tracer for estimating brain SERT levels. The results depict no

differences compared to HC. However the findings are preliminary, since the sample size is too small to exemplify reasonable size for power analysis and the tracer. As mentioned above, evidence from behavioral, neuroimaging and genetic studies suggest an involvement of the serotonergic system in ADHD. The SERT terminates serotonin from the synaptic cleft, therefore withholding a pivotal role in the regulation of serotonergic signaling. The SERT BP_{ND} has been investigated in the past with [11C]DASB and PET in various neuropsychiatric disorders [Spies et al., 2015].

In the last decades neuroimaging investigations have begun to change the conceptual focus from activation paradigms towards connectivity analysis, from univariate, where activation in cue-related regions is explored, to multivariate analysis, where correlations of activation across brain regions are evaluated [Bullmore, 2012]. To disclose a possible involvement of a specific neurotransmitter system in neuropsychiatric disorders, PET imaging has predominantly been used to observe regional availability of a particular transporter or receptor in a specific brain region. Though, through performing interregional correlation analyses, PET imaging has also been applied to explore brain connectivity in HC, major depressive disorder, autism and obsessive-compulsive disorder, Alzheimer's disease and epilepsy [Baldinger et al., 2014; Horwitz et al., 1984; Lee et al., 2008; Morbelli et al., 2013; Vanicek et al., 2016].

The serotonergic system represents one of the chief modulatory neurotransmitter systems in the human brain, where neurons from the raphe nuclei innervate nearly all cortical regions and several subcortical structures. Therefore, serotonin is associated with almost all emotional and cognitive functions. Since the SERT expression is modified via available and released serotonin [Benmansour et al., 2002], investigations on the relation of SERT expression between different brain regions may exemplify a valuable method to understand the function on a more global level of this neurotransmitter system. Studies from our group showed that molecular associations of the serotonergic neurotransmitter system (serotonin-1A receptor and SERT) differed between depressive patients and HC [Baldinger et al., 2014; Hahn et al., 2014; Lanzenberger et al., 2012], implicating that interregional molecular correlation analyses is a promising method to generate more insight to the complexity of neurotransmitter systems and their role in neuronal pathophysiology.

Therefore, we applied [11C]DASB and PET to assess SERT BP_{ND} in SERT rich regions to observe differences in SERT availability between adult patients with ADHD and HC. Furthermore, we performed a correlational analysis, to examine interregional association of SERT binding as an index for interregional molecular balance of serotonergic neurotransmission. We hypothesized that SERT BP_{ND} and interregional molecular associations of SERT availability across brain areas will reflect a characteristic pattern that differs between patients with ADHD and HC.

METHODS

Subjects

Twenty-five adult patients with ADHD (age ± SD; 32.39 ± 10.15; 10 females) and 25 age and sex matched HC (aged 33.74 ± 10.20) were recruited through the ADHD outpatient clinic at the Department of Psychiatry and Psychotherapy, Medical University of Vienna and from the local community via advertisement. Patients were free from psychopharmacologic treatment for at least six months prior to the screening visit while HC were naïve to all psychopharmacologic treatment. Four patients used methylphenidate in the past, one patient atomoxetine and one antidepressant medication. Written informed consent was obtained from all participants after detailed explanation of the study protocol and subjects received financial reimbursement for their participation. This study was approved by the Ethics Committee of the Medical University of Vienna and the General Hospital of Vienna (EK 552/2010).

Medical Examination and Clinical Exploration

Subjects underwent standard medical examination including a general physical and neurological status, electrocardiography and routine laboratory tests at the screening- and final visit in order to ensure physical health. Female participants underwent a urine-pregnancy test at the screening visit and prior to PET measurement. A multidrug-urine test was performed at the screening visit in order to exclude current substance abuse. Participants were interviewed by experienced psychiatrists using Conners' Adult ADHD Diagnostic Interview for DSM IV (CAADID, Conners 1999) to evaluate current and childhood attentional and hyperactivity/impulsivity symptoms and to attest ADHD diagnosis. (ADHD: impulsive symptoms: 20.05± 4.34 hyperactive symptoms: 20.05 ± 4.42; HC: impulsive symptoms: 0.55± 0.92 hyperactive symptoms: 0.35 ± 0.79). For five patients hyperactivity/impulsivity symptoms were not recorded, thus we excluded these patients and their matched HC from this analysis. Structured Clinical Interview for DSM IV Axis I and Axis II disorders (SCID-I, SCID-II) was performed to exclude comorbid psychiatric disorders. Smoking status was recorded and subjects were subdivided into groups best describing their smoking status according to quantity of consumption (non-smokers, five cigarettes/week, five cigarettes/day, five to ten cigarettes/day, ten cigarettes/day, ten to 15 cigarettes/day, 15 cigarettes/day and 20 cigarettes/day; ranks 1-8, respectively). ADHD patients did not significantly differ in smoking status compared to HC (Mann-Whitney U = 161.5, Z=−1.25, P = 0.30). Subjects with PET- or MRI-incompatible implants or in pregnancy or breastfeeding were also excluded.

Data Acquisition

All PET scans were carried out at the Dept of Biomedical Imaging and Image-guided Therapy, Division of

Nuclear Medicine, Medical University of Vienna using a full-ring scanner (General Electric Medical Systems, Milwaukee, WI, USA) in 3D acquisition mode. We applied [^{11}C]DASB [Haeusler et al., 2009], which is currently among the most suitable PET tracers for in vivo SERT quantification as reported previously in detail [Lanzenberger et al., 2012]. A 5 min transmission scan using retractable ^{68}Ge rod sources for tissue attenuation correction was performed prior to the emission scan. Data acquisition started with a bolus i.v. injection. Brain radioactivity was measured in a series of 50 consecutive time frames (12×5 s, 6×10 s, 3×20 s, 6×30 s, 4×1 min, 5×2 min, 14×5 min) with a total measurement time of 90 min after bolus. Acquired data were reconstructed in volumes consisting of 35 transaxial sections (128×128 matrix) using an iterative filtered back-projection algorithm (FORE-ITER) with a spatial resolution of 4.36 mm full-width at half maximum 1 cm next to the center of the field of view. For coregistration, magnetic resonance (MR) images were acquired from all participants on a 3 Tesla (T) Philips scanner (Achieva) using a 3D T1 FFE weighted sequence, yielding 0.88 mm slice thickness and inplane resolution of 0.8×0.8 mm.

Data Quantification

Each time frame of the dynamic PET scan was realigned to the mean of frames with no head motion, identified by visual inspection. Subsequently, each summed image (PET integral image from realigned data) was coregistered (rigid body transformation) to each subject's MRI using a normalized mutual information algorithm implemented in SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm/). Individual MRIs were spatially normalized to the T1-weighted MRI template provided in SPM. Resulting transformation matrices were applied to the coregistered PET images, warping them into MNI standard space. Parametric images of BP$_{ND}$ [Innis et al., 2007] values were calculated using the multilinear reference tissue model with two parameters (MRTM2) implemented in PMOD image analysis software, version 3.509 (PMOD Technologies Ltd., Zurich, Switzerland; http://www.pmod.com). Thalamus was used as the receptor-rich region and cerebellar grey matter as the reference region because it contains negligible availability of SERT and has been demonstrated to represent the optimal reference region for [^{11}C]DASB [Parsey et al., 2006].

Regions of Interests (ROIs)

Selected ROIs included SERT rich brain regions, based on previous PET, in vivo, human brain studies [Savli et al., 2012], including the anterior cingulate cortex, amygdala, dorsal raphe nuclei as well as the hippocampus, insula, precuneus, posterior cingulate cortex, striatum and thalamus. Binding potential values were extracted from an automated anatomical labelling (AAL)-based atlas [Savli et al., 2012], including manually delineated ROIs for the dorsal and medial raphe nucleus.

Statistical Analysis

Data was analysed using linear mixed models for the outcome measure SERT BP$_{ND}$ with group, sex, and ROI as fixed factors, with ROI as repeated factor, and subjects and matched participant pairs as random factors. Fixed effects were included in the model in a multifactorial approach whereas interaction effects were dropped in case of non-significance. In case of significant interactions or main effects, post-hoc pairwise comparisons were computed and Bonferroni corrected for multiple comparisons. In a second exploratory approach to examine the effects of age and smoking status, a mixed model was calculated using a stepwise procedure with backward elimination, i.e., starting with all candidate variables (including subject groups and ROI) followed by a stepwise deletion of interactions and variables with largest P-values. Finally, mixed models using the same procedure were applied to investigate the effects of clinical variables CAARS-inattentiveness and CAARS-hyperactivity/impulsivity. According to Akaike's information criterion [Akaike, 1974], repeated measurements were modelled using the diagonal structure. SPSS version 19.0 for Windows was used for statistical computations. The two-tailed significance level was set at 0.05.

Interregional molecular association matrices were calculated between each ROI pair using Spearman's rank correlation coefficient ($\Delta\rho$) for each group separately. For the assessment of statistically significant differences ($P < 0.05$) in balance between patients with ADHD and HC, correlation matrices were transformed using Fisher's r-to-z-transformation and a 10,000 fold permutation test was performed. Results were Bonferroni correction for multiple comparisons.

RESULTS

Linear mixed models analysis revealed a main effect of ROI ($F_{800.22} = 72.08$, $P < 0.001$) and of subject group ($F_{29.35} = 261.37$, $P < 0.001$; Table 1; Fig. 1), but no main effects for sex ($F_{1.21} = 21.26$, $P = 0.1$) and no interaction effects (all $P > 0.1$). Post-hoc pairwise comparisons revealed significant attenuated SERT BP$_{ND}$ in patients with ADHD compared to HC in the striatum ($P = 0.029$; uncorrected) as well as trend in the anterior cingulate cortex and insula ($P = 0.066$ and $P = 0.085$; uncorrected). After applying Bonferroni correction for multiple comparisons, we were not able to detect any significant differences (Table I).

When investigating the potential effects of age, mixed models analysis for ROI SERT BP$_{ND}$ based on AAL atlas revealed an interaction effect between ROI and age ($F_{3.53} = 69.79$, $P < 0.002$), in addition to a main effect of ROI main effect of age ($F_{7.15} = 21.26$, $P = 0.014$). Post-hoc
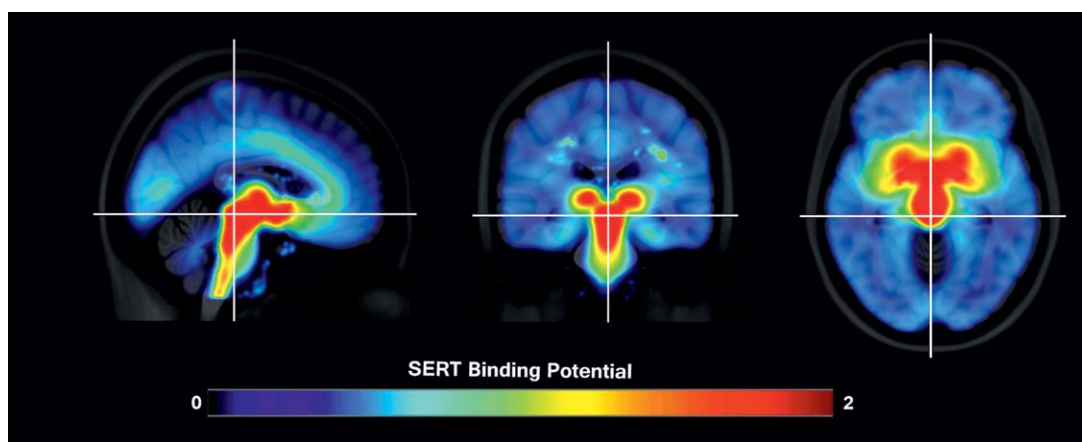
Figure 1.
Average [^{11}C]DASB distribution in 25 patients with ADHD normalized to MNI T1 template. Highest SERT BP$_{ND}$ is found in the dorsal raphe nuclei ROIs. The color table represents binding potential at each voxel, blue indicates lowest and red highest SERT BP$_{ND}$. Crosshair is set on the dorsal raphe nuclei in MNI space. [Color figure can be viewed at wileyonlinelibrary.com]

correlation analyses between regional SERT BP$_{ND}$ and age revealed negative correlations in the thalamus and insula ($R^2 = 0.284$, $R^2 = 0.167$, $Ps < 0.05$; Bonferroni corrected; Fig. 2). Furthermore, negative correlations in the anterior cingulate cortex ($R^2 = 0.128$), posterior cingulate cortex ($R^2 = 0.119$) and the precuneus ($R^2 = 0.129$) were detected, however not significant after Bonferroni correction. These correlations did not differ between HC and ADHD patients. Smoking status had no effect on SERT BP$_{ND}$ nor did they lead to any significant interactions. Additionally, no main or interaction effects were observed for clinical variables (CAARS-Inattentiveness, CAARS-Hyperactivity/Impulsivity) and SERT BP$_{ND}$.

TABLE I. SERT BP$_{ND}$ by region of interest

Region of interest	HC	ADHD	p-value
Anterior cingulate cortex	0.318 ±0.071	0.278 ±0.076	0.066
Amygdala	1.025 ±0.158	0.958 ±0.181	0.183
Dorsal raphe nucleus	3.522 ±0.653	3.463 ±0.526	0.697
Hippocampus	0.605 ±0.127	0.563 ±0.118	0.194
Insula	0.558 ±0.103	0.518 ±0.101	0.085
Precuneus	0.240 ±0.052	0.198 ±0.070	0.723
Posterior cingulate cortex	0.246 ±0.078	0.228 ±0.085	0.433
Striatum	1.748 ±0.248	1.603 ±0.209	0.029*
Thalamus	1.880 ±0.266	1.772 ±0.256	0.096

Mean SERT BP$_{ND}$ and standard deviations are listed from automated AAL, including manually delineated ROI dorsal raphe nuclei for patients with ADHD and HC.
*Marks significant differences between patients with ADHD and HC, though, after Bonferroni correction for multiple comparisons, differences are not significant different.
AAL: anatomical labelling atlas; ADHD: attention deficit/hyperactivity disorder; HC: healthy control subjects; SERT BPND: serotonin transporter binding potential; ROIs: regions of interest.

When comparing interregional SERT BP$_{ND}$ correlations between patients with ADHD and HC, we found a significant difference in the correlation of precuneus with amygdala, hippocampus, insula, DRN and ACC, of the hippocampus with insula and ACC as well as of the PCC and the ACC. Only the differences in interregional molecular correlations of precuneus with hippocampus survived Bonferroni correction for multiple comparisons ($P = 0.0324$; see Table II, Figs. 3 and 4).

DISCUSSION

In this cross-sectional PET study we aimed to investigate SERT availability in adult, medication free patients with ADHD. When comparing groups, we observed lower SERT availability for all ROIs pooled together in patients with ADHD compared HC. For separate brain regions and after correction for multiple comparisons, results show no significant differences in SERT BP$_{ND}$ between patients with ADHD and HC. When comparing interregional SERT BP$_{ND}$ correlations between groups, we found a significant increase for interregional SERT BP$_{ND}$ correlations of the precuneus with hippocampus. In addition, we observed a negative correlation for SERT BP$_{ND}$ and age for patients and HC in the thalamus and the insula.

Previously published PET and SPECT imaging studies found no changes in SERT availability between patients with ADHD and HC [Hesse et al., 2009; Karlsson et al., 2013]. Though, findings are preliminary and should be interpreted with caution, since Karlsson et al. investigated SERT BP$_{ND}$ in eight patients with ADHD, a sample size insufficient in power to detect putative differences [Karlsson et al., 2013]. Another study observed SERT availability with [^{123}I]FP-CIT, a SPECT radiotracer showing only moderate specificity to the SERT in subcortical regions [Hesse et al., 2009]
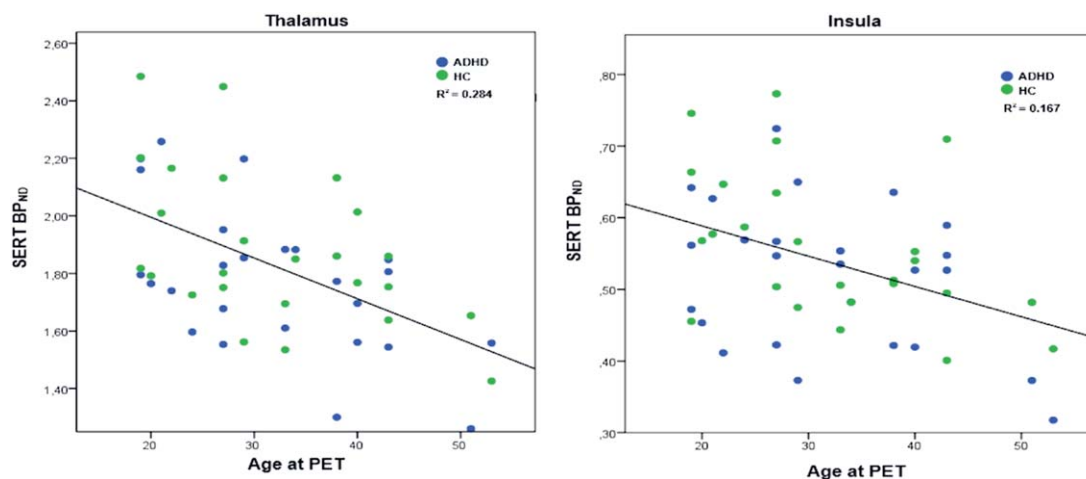
Figure 2.

Negative correlation of SERT BP_{ND} and age in the thalamus and insula in both patients with ADHD and HC. Scatterplots showing a significant negative correlation between SERT BP_{ND} and age in the thalamus ($R^2 = 0.284$) and insula ($R^2 = 0.167$). ROIs were extracted from automated AAL. Age is given in years, significance level was set to $P < 0.05$ and results were Bonferroni corrected for multiple comparisons. AAL: anatomical labelling atlas; ADHD: attention deficit/hyperactivity disorder, SERT BP_{ND}: serotonin transporter binding potential, ROIs: regions of interest. [Color figure can be viewed at wileyonlinelibrary.com]

and demonstrated no alteration between patients and HC. We found attenuated SERT binding in patients with ADHD at uncorrected P-value in the striatum, a region that has been found to exhibit ADHD specific morphological and functional alterations [Plichta et al., 2009; Qiu et al., 2009]. Elevated SERT availability has been shown to be correlated with cognitive performance in the caudate as well as in other brain regions in HC [Madsen et al., 2011] whereas a negative association has been found between SERT binding and impulsive behavior in suicide attempters [Ryding et al., 2006]. Our finding may suggest a contribution of the SERT to the pathophysiology in ADHD, which may be key for impulsive symptoms. Nevertheless, and in line with previous SERT imaging in ADHD, we found no differences in SERT BP_{ND} after correction for multiple testing in patients with ADHD in comparison to HC.

The findings further demonstrate a decrease of SERT BP_{ND} with increasing age in the thalamus, insula, precuneus and anterior and posterior cingulate cortex in patients and HC. This validates previous SERT investigations [Hesse et al., 2003; Yamamoto et al., 2002] as well as PET studies observing the noradrenergic transmitter system [Ding et al.,

TABLE II. Significant differences in interregional molecular correlations of the SERT BP_{ND}

Region of interest	$\Delta\rho$	P-value	P-value Bonferroni corrected
Precuneus—amygdala	0.3846	0.0206[a]	0.7416
Precuneus—hippocampus	0.74308	0.0009[a]	0.0324[b]
Precuneus—insula	0.52231	0.0072[a]	0.2592
Precuneus—dorsal raphe nucleus	0.68	0.0134[a]	0.4824
Precuneus—anterior cingulate cortex	0.50923	0.0077[a]	0.2772
Hippocampus—posterior cingulate cortex	0.42	0.0218[a]	0.7848
Hippocampus—insula	0.30385	0.0243[a]	0.8748
Anterior cingulate cortex—posterior cingulate cortex	0.42769	0.0259[a]	0.9324

We observed significant stronger interregional associations of SERT BP_{ND} between the listed ROIs in patients with ADHD and healthy control subjects (Spearman's delta rho; $P < 0.05$; corrected for multiple comparisons).
[a]Marks significant differences between patients with ADHD and HC.
[b]Marks significant differences between patients with ADHD and HC after Bonferroni correction for multiple comparisons.
ADHD: attention deficit/hyperactivity disorder; HC: healthy control subjects; SERT BP_{ND}: serotonin transporter binding potential; ROIs: regions of interest.
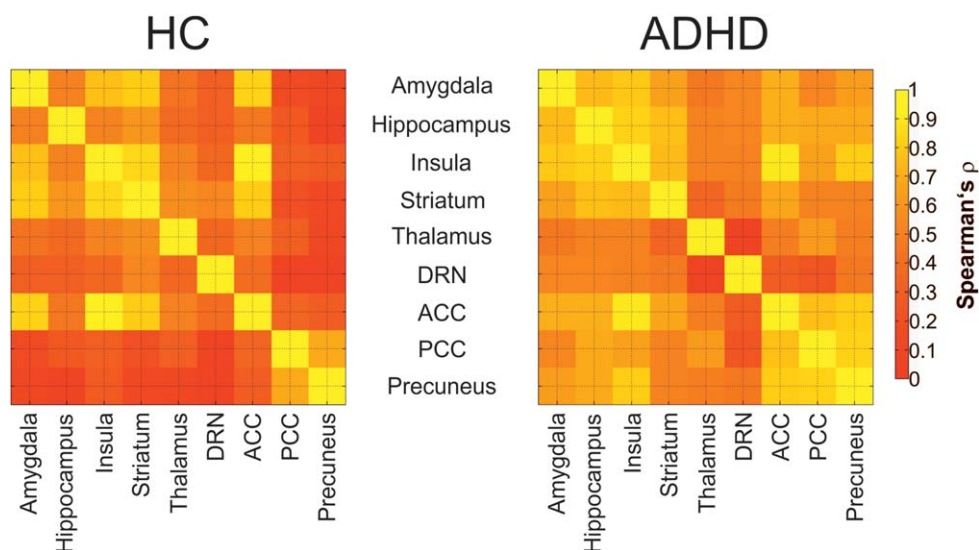
Figure 3.

Molecular interregional molecular correlations of patients with ADHD and HC. Left map shows the correlation (Spearman's ρ) of SERT BP$_{ND}$ in HC indicating interregional differences in functional coupling. Right map denote the condition in patients with ADHD. The color table represents the strength of interregional associations, red indicates lowest and yellow highest interregional associations. ADHD: attention deficit/hyperactivity disorder, SERT BP$_{ND}$: serotonin transporter binding potential, ROIs: regions of interest. HC: healthy controls. [Color figure can be viewed at wileyonlinelibrary.com]

2014; Vanicek et al., 2014], which demonstrated a negative correlation of monoaminergic transporters with age in HC as well as in patients with ADHD.

In addition to the comparison of SERT BP$_{ND}$ between groups, we performed an interregional molecular correlational analysis to evaluate associations of SERT BP$_{ND}$ between the selected ROIs. Our approach is similar to MRI studies, where structural and functional connectivity analyses aim to capture the complexity of large-scale brain networks and findings show widespread and distinct alterations in connectivity in ADHD [Matthews et al., 2014]. These methods were adapted to PET imaging in order to explore if interregional correlations of SERT mirror morphological correlates in the pathophysiology of ADHD. The assumption that regional up- or down-regulation of a single protein, such as the SERT, might be sufficient to differentiate healthy from disordered brains may seem oversimplifying. Therefore, this approach might allow for an even more precise understanding of inherent specificities of the serotonergic system rather than simply comparing transporter binding in various regions between subject groups.

Using this interregional molecular correlational analysis we found significant interregional differences of SERT BP$_{ND}$ correlations for the precuneus and the hippocampus. The serotonergic system projects from raphe nuclei to the precuneus and the hippocampus, therefore modulating regional and network specific function of these brain regions. The precuneus is part of the posterior components of the default mode network, a network that is activated during no-goal directed processes, which has been shown to be dysfunctional in ADHD [Castellanos et al., 2008]. Using resting-state fMRI, altered functional connectivity between the precuneus and other brain regions, specifically the ventromedial prefrontal cortex, a region which is highly innervated and modulated by serotonin action, has been demonstrated. In addition, the precuneus has also been found to be involved in timing functions, exhibiting increased activation patterns in patients with ADHD relative to HC using fMRI [Hart et al., 2012]. Timing deficits have been observed in patients with ADHD and linked to impulsiveness [Rubia et al., 2009].

The hippocampus is associated with learning and memory and is implicated in encoding novel stimuli, processing spatial information as well as in attention [Goldfarb et al., 2016; Jarrard, 1995; Kaplan et al., 2014; Van Petten, 2004]. Being a component of the limbic region, the hippocampus is highly modulated by serotonergic neurotransmitter system, receiving projections from midbrain serotonergic cells [Hensler, 2006]. During a decision-making task, measured with [^{15}O]H$_2$O and PET, regional blood flow has been found to be reduced in the hippocampus in patients with ADHD [Ernst et al., 2003]. The altered activation in the hippocampus as well as in other regions in ADHD is interpreted as a diminished involvement of brain regions associated with complex cognitive-emotional functions. A MRI study found reduced hippocampal volume and connectivity of the hippocampus with the prefrontal cortex, whereas structural findings were associated
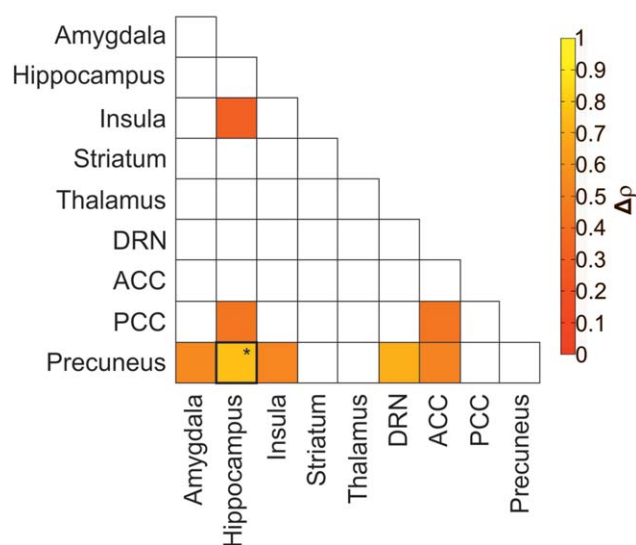
Figure 4.

Difference in the interregional SERT balance between patients with ADHD and HC subjects. Color marked squares demonstrate significant differences in interregional SERT coupling in patients with ADHD compared to HC subjects ($P < 0.05$). After Bonferroni correction for multiple comparisons, we found significant differences in interregional correlations of precuneus with hippocampus ($P = 0.0324$), marked with *. The color table represents the difference in interregional associations (in Spearman's delta rho), red indicates lowest and yellow highest interregional associations. ADHD: attention deficit/hyperactivity disorder, SERT: serotonin transporter, ROIs: regions of interest. [Color figure can be viewed at wileyonlinelibrary.com]

with depressive symptoms [Posner et al., 2014]. Though other structural MRI investigations have showed inconclusive data in ADHD, depicting higher or no differences in hippocampal volume between patients with ADHD and HC [Castellanos et al., 1996; Plessen et al., 2006].

Imaging and behavioral studies have demonstrated that serotonergic neurotransmission affect impulsive behavior [Dalley and Roiser, 2012], motor planning and sensory perception [Biskup et al., 2016] and modulates the default mode network [Hahn et al., 2010]. Recently, it has been found that, compared to HC, patients with ADHD show elevated functional connectivity of the default mode network and attenuated functional connectivity in a state of diminished brain serotonin levels, evoked through acute tryptophan depletion [Biskup et al., 2016]. We found a higher molecular correlation of the SERT between the precuneus and the hippocampus in patients with ADHD and in general lower correlations in HC, which may reflect higher impulsivity in patients and might be explained by a more diverse, region specific modulated serotonergic system in HC and by more rigid and less variable serotonergic signaling in ADHD.

This PET study has limitations that compromise the interpretation of its results. Regarding group differences in

regional SERT binding a main effect was observed, but only trends for significant differences were obtained in separate brain regions. Although the sample size of this study is common for investigations with PET [Kranz et al., 2015; Volkow et al., 2007], it is still possible that more subjects are required to identify more subtle differences. On the other hand, the significance in the main effect but not for single ROIs might be driven by a more reliable variance estimate for the former one. Next to the thalamus and the insula, we found an association between age and SERT binding in the anterior cingulate cortex, posterior cingulate cortex and the precuneus, though not significant after applying Bonferroni correction. Previous PET studies found a decline in SERT with age in the raphe nuclei, though, we did not observe an age-related decline of SERT in the dorsal raphe nuclei. The dorsal raphe nuclei is relatively small structures in the midbrain where signal to noise ratio is rather low. Therefore, it is possible that there is an age-related decline in SERT in this region, although we did not detect an association. In addition, no blood sampling was carried out in this study. This impedes the evaluation of potential differences in the cerebellum, which was however suggested to represent an optimal reference region [Parsey et al., 2006].

CONCLUSION

In conclusion, we observed altered interregional SERT BP_{ND} correlation of the precuneus and the hippocampus in patients with ADHD, underlining the involvement of these brain areas in the pathophysiology of ADHD. On the other hand, SERT binding does not differ after applying correction for multiple comparisons on a regional level between patients with ADHD and HC. Given the fact that the SERT expression is modulated by regional serotonergic release, our results are compatible with alterations of interregional coupling within the serotonergic system in ADHD.

ACKNOWLEDGMENTS

DISCLOSURE OF BIOMEDICAL FINANCIAL INTERESTS AND POTENTIAL CONFLICTS OF INTEREST

All authors declare no competing financial interests in relation to the work described. Without any relevance to thisƒ work, M Hacker has received conference speaker honoraria from Covidian, GE Healthcare, IBA and

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