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In-vivo serotonin transporter availability and somatization in healthy subjects

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ABSTRACT

Dysregulation of the central serotonergic system is implicated in somatization, which can lead to manifest mental disease. However, neuroimaging studies on serotonin transporter (SERT) availability and somatoform symptoms as assessed by the Symptom Checklist 90 Revised (SCL-90-R) are sparse and reveal inconsistent results. The aim of this study was to explore for the first time the relationship between SERT and somatoform symptom expression in healthy volunteers including the analysis of the SERT-LPR genotype. Fourteen healthy subjects (age 36.07 ± 7.22 years, 9 females) completed the SCL-90-R, underwent [^{11}C]DASB PET and were genotyped on the same day. SERT binding potentials (BP_{ND}) were quantified with the multilinear reference tissue model (MRI coregistration). The BP_{ND} of the right orbitofrontal cortex (OFC) correlated positively with the somatization subscale. The SERT availability of the right OFC correlated significantly with the obsessive–compulsive subscale and the degree of anxiety was associated with the BP_{ND} of the right hippocampus. No main genotype effect on regional SERT availability or on the association between SERT BP_{ND} and the respective SCL-90-R subscales was observed. Our findings document a positive correlation between frontal SERT availability and the severity of somatoform symptoms prior to the onset of disease.

1. Introduction

Dysregulation of the serotonergic system is thought to play a role in several psychopathological states including somatization, obsessive-compulsiveness and anxiety, which can represent mental disturbances at sub-threshold levels and thus susceptibility to disease manifestation.

The classification system of mental disorders has become more dimensional and the use of standardized assessment methods has grown rapidly (Myers & Winters, 2002). Among self-report instruments developed to assess current psychopathology, one of the most extensively used is the Symptom Checklist 90 Revised (SCL-90-R) (Schmitz, Hartkamp, & Franke, 2000). It comprises nine primary dimensions (somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism) and serves not only as a screening instrument (Starcevic, Bogojevic, & Marinkovic, 2000) but also as an outcome measure (Tarescavage & Ben-Porath, 2014). In light of the fact that the serotonergic system is the most extensively studied network in psychiatry, the SCL-90-R serves as tool for symptom evaluation of its most strongly associated conditions such as somatization (Anderson, Berk, & Maes, 2014), depression (Nikolaus, Hautzel, Heinzel, & Muller, 2012), obsessive-compulsiveness (Hesse et al., 2011), anxiety (Marazziti et al., 2015) and hostility (Hakulinen et al., 2013).

Abbreviations: BP_{ND}, binding potential; FWHM, full-width at half maximum; GSI, global severity index; L-allele, long allele; MRI, magnetic resonance imaging; MRTM2, multilinear reference tissue model 2; OCD, obsessive–compulsive disorder; OFC, orbitofrontal cortex; PCR, polymerase chain reaction; PSDI, positive symptom distress index; PST, positive symptom total; PET, positron emission tomography; PFC, prefrontal cortex; SERT, serotonin transporter; SERT-LPR, serotonin transporter promoter length polymorphism; S-allele, short allele; SPECT, single photon emission computed tomography; SSRI, serotonin reuptake inhibitor; SCL-90-R, Symptom Checklist 90 Revised; VOI, volume-of-interest.

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Somatic symptom disorder, whose pathophysiology is poorly understood, is characterized by somatic symptoms that are either very distressing or result in significant disruption of function; yet the key feature is not the symptoms per se but the excessive and disproportionate dimension of those symptoms (Association, 2013). Converging lines of evidence suggest that somatization coincides with a decreased serotonergic tonus (Maes, Galecki, Verkerk, & Rief, 2011; Rief et al., 2004). The hypothesis that somatization is linked to the serotonin system is also supported by the clinical effect of serotonin reuptake inhibitors (SSRIs) reducing symptom severity (Somashekar, Jainer, & Wuntakal, 2013). However, the association of symptom severity in somatization and serotonergic dysfunction is not established.

Neuroimaging studies investigating the physiological target of SSRIs, the serotonin transporter (SERT), focusing on somatization are scare and yield inconsistent results. In healthy subjects, a significant negative correlation between somatization and mesencephalic SERT availability, particularly in males, has been reported (Chou et al., 2012). Notably, this [^{123}I]ADAM single photon emission computed tomography (SPECT) study restricted its focus to one brain region, the midbrain, only. The same group has previously reported on a negative correlation between hostility and mesencephalic SERT availability applying the same radioligand and midbrain-region-only approach (Yang et al., 2007). A recent [^{11}C]DASB positron emission tomography (PET) study investigating eleven cortical and subcortical brain regions in a small subsample of seven healthy controls, however, revealed no significant association between SERT availability and symptom severity as displayed by the SCL-90-R subscale values (Hammoud et al., 2010).

Further, it has been suggested that personality disorder traits are associated with the functional serotonin transporter promoter length polymorphism (SERT-LPR) (Blom et al., 2011; Kim, Kim, Lee, Kim, & Kim, 2006). Genetic association studies regarding somatization have been inconsistent, reporting no influence of the SERT-LPR (Koh, Choi, Lee, & Han, 2011) or a linkage to the high transcriptional long allele (L-allele) of long/short polymorphism in the serotonin gene promoter region (Hennings, Zill, & Rief, 2009; Maes et al., 2011; Rief et al., 2004). Again, contrasting data revealed that individuals carrying the short allele (S-allele) display a higher intensity of somatization when facing life adversities (Veletza et al., 2009).

Recently, the hypothesized serotonergic deficit in somatization has been coupled to being an integral part of susceptibility to, and course of, neurological illnesses with an inflammatory component (Anderson & Maes, 2014). Additional input, other than the case–control approach, which makes up the majority of the published literature in neuroimaging, is helpful to denote individual differences in serotonergic neurotransmission regarding the level of somatization. Further, such an approach offers improved phenotypic definition when compared to the manifested disease state. Based on the results outlined above, we hypothesized that the degree of somatization is related to central serotonergic activities, even in healthy individuals. We used [^{11}C]DASB PET in conjunction with genetic analysis of the SERT-LPR to test for associations between in-vivo SERT availability and SCL-90-R measures.

2. Materials and methods

2.1. Subjects

Fourteen healthy subjects (mean age 36.1 ± 7.2 years, range 21–49 years; body mass index 22.5 ± 2.6 kg/m^2; 9 females) were included in the study. All subjects were seen by a psychiatrist and received a general physical examination. Exclusion criteria were past or present history of alcohol misuse and/or illicit drug abuse, current or past neurological or psychiatric disease, epilepsy, migraine, cerebral seizures in previous medical history (or in history of the family), neurosurgical interventions in the past, pregnancy, hypertension, diabetes or other medical conditions that may alter brain function as well as contraindications for magnetic resonance imaging (MRI, e.g. implanted ferro-magnetic devices, claustrophobia).

The study was approved by the ethics committee of the Medical Faculty of the University of Leipzig and was in accordance with the Helsinki Declaration. After complete description of the study to the subjects, written informed consent was obtained.

2.2. Genotyping

As previously described (Hesse et al., 2011), we assessed the SERT-LPR genotype with polymerase chain reaction (PCR) and a standardized procedure with primers synthesized by Invitrogen (UK), and additionally, the primers described by Heils et al. (1996).

2.3. Measure

The psychological testing was performed prior to the PET scan on the same day. In this study the German SCL-90-R, a reliable and validated scale (Derogatis & Cleary, 1977; Schmitz et al., 2000), was used. It is a 90-item multidimensional questionnaire where each item is rated on a five point Likert scale, ranging from “not at all” (0) to “extremely” (4). Subsequently, the answers are combined in nine primary dimensions (somatization, obsessive–compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism) and three global indices (global severity index (GSI), positive symptom total (PST) and positive symptom distress index (PSDI)). We reported on the SCL-90-R scores as raw values and T scores (Table 1). In order to rate the symptom severity clinically, the SCL-90-R simple mean values are converted to standard T scores ranging from a minimum of 20 to a maximum of 80 by referring to population-based norms, which are provided by the test manual (Franke, 2014). A T score of 50 represents the mean T score of the respective normal population and a T score range from 40 to 60 represents the normal range as defined

Table 1
Demographic, psychometric and selected SERT binding potential (BP_{ND}) data.

Demographics		
Age (years)		36.07 ± 7.22
Body mass index (kg/m^2)		22.49 ± 2.59
Beck Depression Inventory		2.43 ± 2.74
Edinburgh Handedness Inventory		13 right-handed (92.9%)
		1 ambidextrous (7.1%)
SERT genotype		
SL-Carrier		8 SL (57.1%)
LL-Carrier		6 LL (42.9%)
Subscales of the SCL-90-R		
	Raw scores	T scores
		Normal range 40–60
Global severity index	0.11 ± 0.12	42.14 ± 7.00
Positive symptom total	8.14 ± 7.34	42.36 ± 6.38
Positive symptom distress index	1.14 ± 0.17	45.93 ± 6.60
Somatization	3.64 ± 2.73	49.43 ± 5.56
Anxiety	0.71 ± 0.83	44.57 ± 5.68
Obsessive–compulsive	0.93 ± 1.98	40.86 ± 6.72
Interpersonal sensitivity	0.57 ± 1.22	41.93 ± 5.58
Depression	1.36 ± 2.65	43.07 ± 7.00
Hostility	1.14 ± 2.63	46.57 ± 8.54
Phobic anxiety	0.29 ± 1.07	45.21 ± 4.48
Paranoid ideation	0.50 ± 0.94	43.50 ± 4.85
Psychoticism	0.14 ± 0.36	44.43 ± 2.95
Selected SERT BP_{ND}		
Right orbitofrontal cortex		0.41 ± 0.10
Right hippocampus		0.52 ± 0.13

Data are shown as mean ± standard deviation or as percentage (%).