Serotonin transporter association between dorsal raphe and ventral striatum is diminished in major depression

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BACKGROUND

One of the key symptoms in patients with major depressive disorder (MDD) is the lack of motivation and hedonic experience. Besides the dopaminergic system, the neurotransmitter serotonin plays a pivotal role in reward processing [1]. Furthermore, reduced levels of serotonin in MDD have been suggested to emerge from high synaptic clearance by increased expression of the serotonin transporter (SERT) [2]. Still, local investigations of the SERT for specific brain regions have led to varying results depending on the clinical syndrome [2].

OBJECTIVE

In contrast to a regional evaluation, we aimed to investigate differences between MDD patients and controls on a network level by assessment of interregional associations in SERT binding.

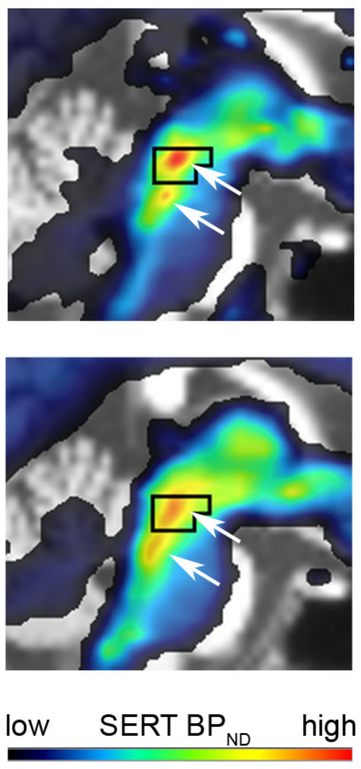

Figure 1: Region of interest definition for the midbrain dorsal raphe nucleus. White arrows indicate differentiation between dorsal and median raphe nuclei.

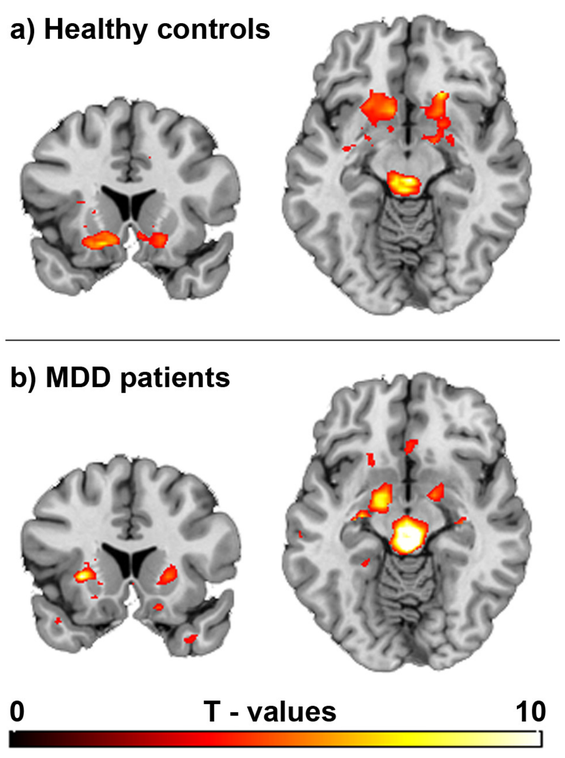

Figure 2: Associations in SERT binding between the midbrain dorsal raphe nucleus and serotonergic projection areas for **a)** healthy controls and **b)** MDD patients (p<0.001 uncorrected, left is right).

METHODS

SUBJECTS: 20 outpatients with MDD (41.4±8.7 years, 13 female, age of onset = 34.7±12.7 years, $HAMD_{17}$ = 20.0±3.9) and 20 healthy controls (31.3±9.7 years, 7 female) were included in this study.

POSITRON EMISSION TOMOGRAPHY (PET): Each subject underwent a single PET measurement using the radioligand [^{11}C]DASB (injected dose = 259.8±76.5 MBq). Scan time was 90min and spatial resolution was 4.36mm full-width at half-maximum.

DATA PROCESSING: Image preprocessing was done in SPM8, which included motion correction and spatial normalization to MNI-space. Quantification of SERT binding potential (BP_{ND}) was carried out voxel-wise with the multilinear reference tissue model 2 in PMOD3.3. Here, the striatum and cerebellar gray taken from an atlas served as receptor-rich and -poor regions, respectively. Voxel-wise maps were used as representation of SERT binding in serotonergic projection areas. Additionally, a midbrain region of interest (0.83cm^3, 4 axial slices, Fig 1) was used to extract SERT binding within the dorsal raphe nucleus (DRN) as indicator of midbrain serotonergic neurotransmission.

STATISTICAL ANALYSIS: The association of SERT binding between the DRN and projection areas was computed by voxel-wise linear regression with the DRN as independent variable and voxel-wise maps as dependent variable. Group differences between patients and controls were assessed by an ANCOVA. Statistics were corrected for multiple comparisons with the family wise error rate (FWE) on a voxel-level.

RESULTS

Both study populations exhibited only positive SERT associations between DRN and projection areas. For controls, these were strongest in the ventral striatum and amygdala (Fig 2a). In patients however, the correlation pattern was most pronounced in the putamen, pallidum, amygdala, thalamus, (para)hippocampus, and insula (Fig 2b).

Direct comparison between the two groups showed significant differences only in the right (t=5.85, p<0.05 FWE) and left (t=5.07, p<0.1 FWE) ventral striatum (Fig 3). More precisely, the decreased regression coefficient in patients (β=0.08-0.12) as compared to controls (β=0.49-0.55) indicates that a unit change in DRN SERT binding has 4.6-6.1 times less effect on ventral striatum SERT binding in patients. Furthermore, the explained variability was 2.7-6.6 fold lower in patients (R^2=0.11-0.24) than in controls (R^2=0.66-0.72). Correcting for sex (t=5.74 and 5.04, left and right ventral striatum) and age (t=5.56 and 4.79) did not change these group differences.

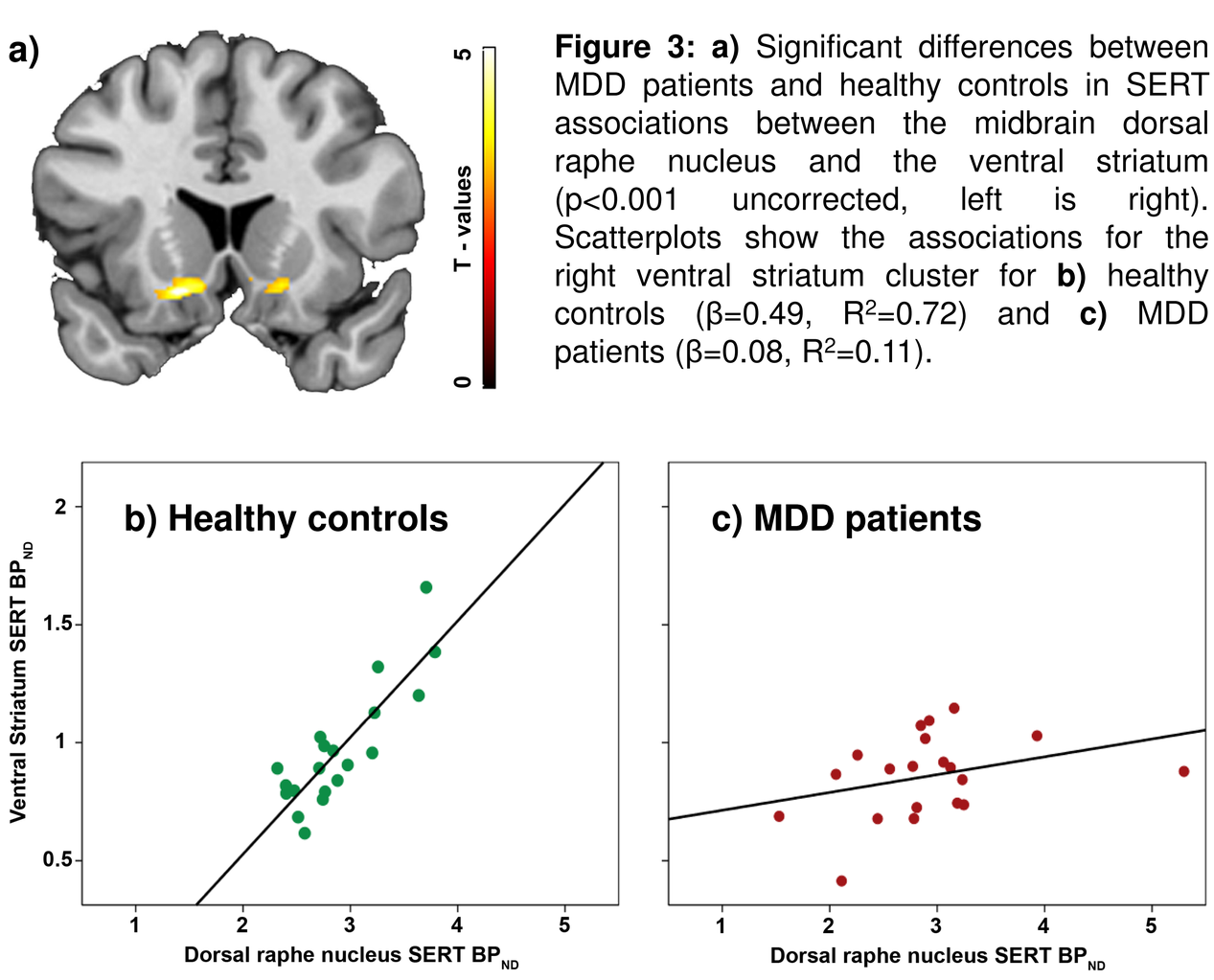

Figure 3: a) Significant differences between MDD patients and healthy controls in SERT associations between the midbrain dorsal raphe nucleus and the ventral striatum (p<0.001 uncorrected, left is right). Scatterplots show the associations for the right ventral striatum cluster for **b)** healthy controls (β=0.49, R^2=0.72) and **c)** MDD patients (β=0.08, R^2=0.11).

CONCLUSIONS

Using an interregional approach we observed a decreased association in serotonin transporter binding between midbrain dorsal raphe and ventral striatum in patients with major depression as compared to controls. As the ventral striatum represents a key region in reward processing [1], this may complement the biological mechanisms of anhedonia in major depression. The observed alterations in serotonergic neurotransmission may however be accompanied by further changes in monoamine oxidase A [3] as well as serotonin-1A [4] and -1B receptors [5]. Nevertheless, this work emphasizes that topological differences in neurotransmitter binding sites [2] may be complemented by investigation on a network level [6].

DISCLOSURE

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