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Title Associations between cognition and serotonin receptor 1B binding in patients with major depressive disorder – a pilot study

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Abstract
The neurotransmitter serotonin has been widely implicated in the pathophysiology of major depressive disorder (MDD). In animal studies and human neuroimaging studies, involvement of the serotonin receptor 1B (5-HT1BR) in MDD and memory performance has been reported. However, the role of the 5-HT1BR in cognitive functions affected in MDD remains to be clarified. Ten patients with MDD diagnosis were examined with positron emission tomography (PET) and a battery of cognitive tests before and after Internet-based Cognitive Behavioral Therapy (ICBT). The results were compared to ten matched control subjects in order to investigate putative changes in 5-HT1BR availability and cognitive performance. Patients treated with ICBT showed statistically significant improvement relative to baseline in Verbal fluency, both letter and category production. Significant correlations were found between improvement in letter production and changes in 5-HT1BR availability in ventral striatum, between category production and amygdala, as well as between the improvement in Trailmaking test B and change in 5-HT1BR binding in dorsal brainstem, in amygdala and in hippocampus. The results suggest an association between 5-HT1BR binding and improvement in cognitive functioning. Replications in larger-scale studies are required to confirm these findings.

Keywords Key words: 5-HT1BR; Depression; Internet-based CBT; Neuroimaging; Serotonin

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1. Introduction

Major depressive disorder (MDD) has a lifetime prevalence of 11-15 % (Bromet et al., 2011) and is the leading cause of disability worldwide (World Health Organization, 2017). It is a clinically heterogeneous disease of variable course in which the core symptoms, low mood and loss of interest, are related to emotional dysregulation. Recent research has demonstrated that also cognitive impairments play an important role in the symptomatology of MDD (Rock et al., 2014; Trivedi and Greer, 2014). These include reversible dysfunctions that largely normalize after a major depressive episode, that is, visuospatial short term memory function (Behnken et al., 2010), and persistent cognitive impairments remaining after remission, such as attention and executive functions (Rock et al., 2014; Årdal and Hammar, 2011). In a meta-analysis investigating executive function in 375 depressed patients and 481 control subjects, patients were found to perform significantly worse in tasks measuring semantic verbal fluency, cognitive flexibility and impulse inhibition (Wagner et al., 2012). Clinically significant impairments in several cognitive domains including psychomotor speed, attention, visual learning and memory, and executive functions have repeatedly been shown to be associated with MDD (Gallagher et al., 2007; Marazziti et al., 2010; Trivedi and Greer, 2014).

As the biological underpinning of MDD is largely unknown, so are the biological mechanisms mediating the cognitive deficits in MDD. Of the various hypotheses for MDD, the monoamine deficiency hypothesis is the most investigated (Agurell, 1981; Coppen, 1967). The monoaminergic hypothesis is mainly based on observations of clinical effects of antidepressant drugs. The currently most widely used pharmacological treatment for MDD is selective serotonin reuptake inhibitors (SSRIs), which inhibit the serotonin transporter and modify serotonin concentration in the synaptic cleft (Lundberg et al., 2007; Nord et al., 2013; Romero et al., 1996). Additional support for an association between serotonin and depression comes from tryptophan depletion studies showing that acute tryptophan depletion results in increased depressive symptoms in remitted MDD patients and subjects with a family history of MDD (Ruhé et al., 2007).

To date, 14 different receptor subtypes for serotonin have been identified in the mammalian brain. With molecular positron emission tomography (PET), specific receptor and transporter proteins can be quantified in the living human brain. In a majority of PET studies of the serotonin system in patients with MDD, differences in 5-HT_{1A} receptor as well as serotonin transporter

binding compared to control subjects have been found (Gryglewski et al., 2014; Savitz and Drevets, 2013). The serotonin receptor 1B (5-HT1BR) has only recently been investigated in MDD. As a heteroreceptor it regulates the release of neurotransmitters such as dopamine or GABA. As an autoreceptor it is involved in the negative feedback mechanism that controls the release of serotonin (Celada et al., 2013; Ruf and Bhagwagar, 2009). Preclinical studies indicate a role of the 5-HT1BR in various behavioral functions such as locomotor activity and aggression (Ramboz et al., 1996), sleep (Boutrel et al., 1999), learning (Wolff et al., 2003) and learned helplessness (McDevitt et al., 2011).

Human *in vivo* studies of the 5-HT1BR have been scarce, but with PET and the 5-HT1BR radioligand [^{11}C]AZ10419369 correlations have been shown between [^{11}C]AZ10419369 binding in grey matter and creativity fluency both in control subjects and in patients with Parkinson Disease (Varrone et al., 2015). In a study of aggression, a positive correlation was found between trait anger and serotonin 1B receptor binding in striatum (da Cunha-Bang et al., 2016). Also, differences in 5-HT1BR binding have been reported after psychotherapy in depressed patients (Tiger et al., 2014) as well as in comparison to a control group (Murrough et al., 2011; Tiger et al., 2016). Taken together, recent research in both animals and humans suggest a role for 5-HT1BR in several aspects of cognitive function and personality, and in the pathophysiology of MDD. Nevertheless, the relation between cognitive changes in MDD and 5-HT1BR binding still remains to be characterized. The limited success of research on the biological underpinning of MDD has raised questions concerning the definition of biologically relevant phenotypes. Cognitive functions affected in mood disorder has been suggested as examples of intermediate phenotypes more robustly related to biological markers (Hasler et al., 2004). This study was thus designed to explore cognitive domains impaired in MDD and their relation with [^{11}C]AZ10419369 binding.

The aim of this exploratory study was to investigate potential associations between changes in cognitive performance in depression and 5-HT1BR binding, assessed using standardized cognitive tests, positron emission tomography and the radioligand [^{11}C]AZ10419369 in a group of depressed patients before and after treatment with psychotherapy as well as in comparison to matched control subjects.

2. Material and methods

The study was approved by the regional Ethical Review Board in Stockholm, by the Radiation Safety Committee of the Karolinska University Hospital and was carried out in accordance with the Declaration of Helsinki. Written informed consent was obtained from all subjects before participation.

2.1. Recruitment of patients

Ten adult patients with untreated MDD of moderate type (Montgomery Åsberg Depression Rating Scale (MADRS) scores 20-35) according to Diagnostic and Statistical Manual of mental disorders (DSM-IV) were recruited by advertisements in press or by the unit of Internet Psychiatry (IPU) at Psychiatry Southwest, Karolinska University Hospital, Southern Campus in Stockholm, Sweden (Tiger et al., 2014). The diagnosis was assessed by a psychiatrist using the Mini International Neuropsychiatric Interview (MINI). Inclusion criteria were healthy according to medical history, physical examination, blood analysis and magnetic resonance imaging (MRI). Exclusion criteria were: bipolar disorder, current substance abuse, organic brain disorder, pregnancy, current psychopharmacological treatment or MRI abnormalities. Control subjects were recruited by newspaper advertisement or from a website designed for scientific research volunteers. The group consisted of ten healthy participants according to psychiatric history and interviews with MINI or the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders (fourth edition) (for details, see Tiger et al., 2016). They were matching the patients regarding gender and age (±3 years (±4 years for one pair); table 1). The PET data in the current study was drawn from previous studies (Tiger et al., 2016, 2014).

2.2. Study design

Each subject underwent an MRI examination, a PET experiment and a battery of cognitive

tests within two weeks after the MRI scan. PET examinations were performed on the same day or the day before the cognitive testing. For the patients, Internet-based cognitive behavioral therapy (ICBT) was initiated on the same day as the first PET experiment (treatment duration 11.9 ±1.4 weeks), conducted in a routine care setting at the IPU. For the patients, a second PET experiment and set of cognitive tests followed 14±2.2 weeks after treatment initiation. Clinician-rated MADRS was administered at each time of PET (mean score at baseline was 26 and mean score at follow-up was 7.4). Also, self-rated MADRS-S was completed by the patients every week throughout the study. The control subjects did not receive ICBT, but only a second assessment consisting of cognitive testing followed approximately 12 weeks after the first examination. Urine toxicology tests were executed on the day of each PET examination and were negative. The results of the PET experiments in relation to MDD have previously been reported (Tiger et al., 2016, 2014).

2.2.1. Psychological treatment

The psychological approach of cognitive behavioral therapy (CBT) refers to a set of interventions focusing on maladaptive cognitions, behaviors and emotions. The treatment consists of different modules and techniques, such as cognitive restructuring or behavioral activation, to decrease symptoms and increase level of functioning. Internet-based CBT (ICBT) is based on traditional face-to-face CBT protocol but is delivered online with guidance from a therapist via the platform (Hedman et al., 2012). Every week, the patient receives a new module with information, questions relevant to the disorder and homework assignments to complete.

2.3. Assessment of cognitive performance

Cognitive functioning was examined in all subjects on two occasions. The tests were selected to measure cognitive functions specifically affected in MDD (Blanco et al., 2013; Rock et al., 2014; Snyder, 2013). Visuo-constructive memory ability was assessed with Rey Complex Figure Test (RCFT) (Shin et al., 2006) at baseline and Taylor Complex Figure Test (TCFT) at follow-up in order to minimize learning effects. Executive functions were assessed with the subtests letter production and category production in Verbal Fluency (Tombaugh et al., 1999) as well as Trailmaking Test (TMT) A and B (Kortte et al., 2002). General intellectual ability was estimated by the subtest Vocabulary in Wechsler Adult Intelligence Scale, third version (WAIS-III).

2.4. Image acquisition and analysis

All subjects underwent MRI; Signa 1.5T or 3.0T, GE Healthcare, for exclusion of brain pathology and co-registration with PET data. An individual head fixation system was used during PET measurements (Bergström et al., 1981). Each patient was examined twice with PET; ECAT High Resolution Research Tomograph (HRRT, Siemens Molecular Imaging) and the radioligand [^{11}C]AZ10419369 (injected radioactivity: 385.7 ± 30.9 MBq). Brain radioactivity in each PET examination was measured during 93 minutes with a frame sequences ranging from 20 seconds to six minutes. SPM5 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging, U.K.) was used to co-register T1-weighted (T1-w) MRI images to PET images and to segment MRI images. Regions of interest (ROI) were defined according to previous studies (Tiger et al., 2016, 2014) and chosen based on previous literature showing abnormal serotonin marker densities in MDD (Drevets, 2000; Murrough et al., 2011; Savitz and Drevets, 2013): orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), subgenual prefrontal cortex (SPC), amygdala, hippocampus (both dorsal and ventral sub regions), ventral striatum and dorsal brainstem (DBS),

and for reference cerebellum. The ROIs were defined manually on individual MRI images, and later on, transferred into PET images (Varnäs et al., 2011). Binding potential (BP_{ND}) was quantified by the stationary wavelet transform-based parametric mapping framework (S-WAPI) implemented in Matlab R2007b for Windows (Cselényi et al., 2006; Schain et al., 2013; Turkheimer et al., 2003). The cerebellum was chosen as reference region due to its negligible 5-HT1BR density (Table 3) (Tiger et al., 2016, 2014; Varnäs et al., 2001).

2.5. Statistics

Paired samples *t*-tests were applied to compare the results of cognitive performance, and 5-HT1BR binding between the two groups and pre-/post- treatment. Effects of diagnostic group and test occasion on cognitive performance were analyzed by a mixed effects modelling approach for repeated measures, as this allows accommodating missing data and the integration of time-varying factors. Group and time were considered as fixed effects in the model. Cognitive performance and 5-HT1BR binding was related using Pearson's correlation coefficients. For correlations found to be significant in the initial analyses, hierarchical multiple regression models were applied for each group and time point of examination by using each significant cognitive test result as a dependent variable and age, educational level as well as BP_{ND} for each significant ROI as predictors. In order to explore the relationship between differences in cognitive performance and differences in 5-HT1BR binding, the relative change in cognitive performance and 5-HT1BR binding between baseline and follow-up (cognitive performance follow-up – cognitive performance baseline)/cognitive performance baseline=ΔCP; (BP_{ND} follow-up – BP_{ND} baseline)/BP_{ND} baseline=ΔBP_{ND}) as well as between differences in cognitive performance (ΔCP) and clinical change using MADRS (MADRS score follow-up – MADRS score baseline/MADRS score baseline=ΔMADRS) was examined by Pearson's correlation coefficient. All statistical

197 analyses were conducted using SPSS (version 23) for Windows with alpha set at 0.05 (two-
198 tailed).
199
200 **3. Results**
201 The patients were examined twice with PET and all participants were examined twice
202 regarding cognitive testing. Unfortunately, due to missing data, part of the cognitive test results
203 could not be retrieved (Table 2). There were no statistically significant differences in age, global
204 IQ or education between the groups (Table 1 and 2).
205
206 *3.1. Cognitive performance at baseline and follow-up*
207 In the patient group, paired samples t-test revealed a significant improvement from baseline
208 to follow-up in Verbal fluency, both regarding letter (t=-3.14; p=0.02) and category production
209 (t=-2.66; p=0.038), but not in RCFT/TCFT, TMT A or TMT B. In the control group, there was a
210 significant improvement from baseline to follow-up in category production (t=-2.76; p=0.04), but
211 no significant performance differences in letter production, RCFT/TCFT, TMT A or TMT B.
212
213 *3.2. Associations between cognitive performance and 5-HT1BR binding*
214 In the patient group at baseline, Pearson´s correlation coefficient showed a moderate
215 correlation between delayed recall in RCFT and 5-HT1BR binding in the amygdala (r=0.65;
216 p=0.041), ventral striatum (r=0.69; p=0.027) and DBS (r=0.69; p=0.028). A moderate correlation
217 was also found between delayed recognition in RCFT and 5-HT1BR binding in amygdala
218 (r=0.66; p=0.04), ventral striatum (r=0.71; p=0.022) and DBS (r=0.74; p=0.015). No significant
219 correlations between cognitive performance and 5-HT1BR binding were found in the patient
220 group at follow-up (p>0.05).

To control for effect of age and educational level on the observed association between cognitive performance and BP_{ND}, multiple linear regression analyses were undertaken using cognitive test score as a dependent variable and age, educational level as well as regional BP_{ND} as predictors. For the patients at baseline, there were no significant effects of any of the predictors on RCFT, delayed recall.

In the control group at baseline, there were strong correlations between delayed recall in RCFT and 5-HT1BR binding in the OFC (r=0.89; p=0.003) and amygdala (r=0.81; p=0.015). A strong correlation was also found in delayed recognition in RCFT and 5-HT1BR binding in the OFC (r=0.96; p=0.001) and DBS (r=0.83; p=0.021). For other cognitive domains tested, correlations between performance and 5-HT1BR binding were not statistically significant (Supplementary table).

When using multiple linear regression and controlling for age and educational level, the relationship between RCFT, delayed recognition and 5-HT1BR binding in DBS remained statistically significant in multiple regression analyses correcting for the effects of age and educational level (β=10.62; p=0.026). Furthermore, the effect of age on RCFT, delayed recognition was found to be statistically significant (β=-0.30; p=0.013).

3.3. Group differences in cognitive performance at baseline

In RCFT delayed recognition, patients performed significantly better than controls (t=3.62; p=0.011).

3.4. Group differences in cognitive performance at follow-up

In Verbal fluency subtest letter production, patients performed significantly better than the control subjects (t=8.14; p=0.001). There were no significant differences in general intellectual ability estimated with WAIS-III Vocabulary task.

3.5. Effect of time and group on cognitive performance

A linear mixed-effect model analysis revealed significant effect of time on the performance in RCFT and TCFT, delayed recognition (F(1, 26) =6.96, p=0.014), an effect of group on the performance in letter production (F(1, 28) =7.84, p= 0.009) as well as effect of time on category production (F(1, 28) =6.11, p=0.02). No significant interaction effects (time*group) were shown (p>0.05).

3.6. Difference in cognitive performance and 5-HT1BR binding before and after treatment

To examine whether differences in cognitive performance correlated with differences in 5-HT1BR binding between baseline and follow-up in the patient group, the relative change (ΔCP and ΔBP_{ND}, respectively) in each cognitive test result as well as 5-HT1BR binding in each ROI were calculated. Pearson's correlation coefficients revealed significant positive correlations between the improvement in letter production and difference in 5-HT1BR binding in ventral striatum (r=0.79; p=0.033), in category production and amygdala (r=0.76; p=0.049) as well as between the improvement in TMT B and difference in 5-HT1BR binding in DBS (r=0.85; p=0.032), in amygdala (r=0.87; p=0.024) and in hippocampus (r=0.89; p=0.017; Table 4).

3.7. Difference in cognitive performance and clinical change before and after treatment

Within the patient group, Pearson´s correlation coefficient revealed no significant correlations ($p<0.05$) between difference in cognitive performance (ΔCP) and difference in clinical change (ΔMADRS) between baseline and follow-up.

4. Discussion

Previous research in animal models, healthy volunteers and MDD patients suggests a role for 5-HT1BR in major depressive disorder and cognition. For instance, studies show 5-HT1BR binding reduction in DBS (Tiger et al., 2014), ACC, SGPFC and hippocampus (Tiger et al., 2016) as well as in ventral striatum/ventral pallidum (Murrough et al., 2011). In this exploratory study, the relation between cognitive performance in tests sensitive to MDD and 5-HT1BR binding in brain regions suggested to be involved in the pathophysiology of MDD have been investigated.

The result indicates that MDD patients improved in cognitive functioning at follow-up, and that this improvement in cognitive performance was positively correlated to changes in 5-HT1BR binding. In the patient group, improvement in letter and category production had a strong and positive correlation with changes in 5-HT1BR binding in ventral striatum and in amygdala, respectively. Further on, improvement in TMT B was positively correlated to changes in 5-HT1BR binding in the DBS, amygdala, and hippocampus. However, performance in category production improved in both the patient group and control group, indicating a learning effect in this task.

Verbal fluency is a task considered to be sensitive to sustained attention, processing speed, and memory retrieval (Badre et al., 2014; Fossati P, Guillaume le B, Ergis AM, 2003), that is, cognitive functions well known to be impaired in MDD. The molecular mechanisms mediating verbal fluency and associated cognitive functions are not known in detail. However, verbal

fluency is known to correlate with idea fluency, a test previously shown to predict 5-HT1BR binding in average grey matter of control subjects and patients with Parkinson´s disease (Silvia et al., 2013; Varrone et al., 2015). In a recent fMRI study, activation of the ventral striatum was reported to be related to learning and success of memory retrieval strategies (Badre et al., 2014). Although the current study was designed to identify variability over a longer time span, the finding that changes in 5-HT1BR binding in the ventral striatum and in amygdala is associated with improvement in letter and category fluency, taken together with previous data on 5-HT1BR and idea fluency suggests that the serotonin system may have a role in mediating aspects of verbal fluency function.

TMT B measures spatial navigation, sustained attention, psychomotor speed and executive function (Gould et al., 2007; Kortte et al., 2002; Porter et al., 2003; Snyder, 2013), domains known to be impaired in MDD (Rock et al., 2014; Wagner et al., 2012). Serotonin has been suggested to be mediating these symptoms, as for instance improvement in psychomotor speed is a known effect from successful treatment of MDD using SSRIs (Blier et al., 1990; Rosenblat et al., 2015). The DBS encloses a major part of the rostral raphe nuclei where the largest group of serotonergic neurons within CNS are situated, making it a key region for regulation of serotonin transmission, that is, decreased 5-HT1BR binding in DBS may reflect globally increased serotonergic activity affecting cognitive functions measured with TMT B. Regarding the amygdala, it has been shown in meta-analyses of fMRI research that the amygdala of patients with affective disorder is more activated during a task measuring sustained attention compared to controls (Sepede et al., 2014). Rumination, an activity negatively associated with sustained attention, has been shown to be positively associated to increased amygdala reactivity as well as abnormal metabolic activity in the hippocampus in MDD subjects (Mandell et al., 2014). Taken together, the findings suggest that the improved cognitive function related to MDD

313 at baseline and follow-up may be connected to reduced 5-HT1BR binding in limbic structures,
314 such as DBS, amygdala and the hippocampus.

315 In the patient group, both letter and category production improved significantly. These are
316 both measures of the executive function domain and examine sustained attention, concentration,
317 retrieval and speed. Several studies show that the domain of executive function is related to MDD
318 (Gallagher et al., 2007; Wagner et al., 2012). The finding of improved letter production in the
319 patient group is in agreement with previous larger non-imaging studies on MDD and cognition,
320 thus confirming the validity of the cognitive performance results (Biringer et al., 2007; Gallagher
321 et al., 2007; Lee et al., 2012). However, as there was no interaction effect of group and time for
322 any of the tests, a learning effect cannot be excluded, hence, these results suggest caution in the
323 interpretation of the findings.

324 In contrast to previous literature, the present results show that cognitive performance was
325 superior in MDD patients compared to control subjects (Table 2). Previously identified factors
326 explaining this could be the (albeit non-significant) difference in age (Lei et al., 2014; Watanabe
327 et al., 2005), level of education (Grant et al., 2001; Lee et al., 2012) and occupational status
328 (Wang et al., 2006) as well as the relatively small sample size compared to previous studies of
329 cognitive performance in MDD not including molecular imaging (Lei et al., 2014; Wang et al.,
330 2006).

331 The present study has a number of limitations. Even though the sample size may be
332 reasonable for molecular imaging studies, it is smaller than in most neuropsychological studies
333 (Quinn et al., 2012). Moreover, the study has suffered data loss. Both these factors increase the
334 risk of type-II errors and all conclusions, although novel should therefore be seen as preliminary
335 until replicated. It cannot be ruled out that the correlations between cognitive performance and 5-
336 HT1BR binding in 3.2 in part may be driven by age, as an age effect previously has been reported

(Nord et al 2014). Lastly, variations regarding the time aspect may have influenced the results, as a diurnal variability in binding to serotonin markers has been reported (Matheson et al., 2015). Notably, as is evident from Table 4, the significant findings reported were not corrected for multiple comparisons, and should thus be seen as hypothesis generating.

In conclusion, the study indicates a possible association between 5HT1BR binding and cognitive performance in MDD. Future large-scale investigations are required to confirm these findings. Importantly, the results support the feasibility of combining rigorous cognitive performance quantification with molecular imaging pre- and post a therapeutic intervention in order to disentangle putative translational biomarkers of psychiatric disease.

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Declaration of interest

No conflict of interest for any of the authors.

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Table 1
Patient and matched control subject characteristics

	Patients						Matched controls		
Nr	Age	Gender	Education	Hand	Episodes	MADRS	Age	Gender	Education
1	25	Male	13	Right	2	20	29	Male	15
2	51	Female	17	Right	10	35	54	Female	13,5
3	46	Female	15	Right	3	28	46	Female	20
4	68	Female	16	Right	3	24	69	Female	7
5	66	Male	19	Right	3	28	64	Male	15
6	37	Female	15.5	Right	>10	26	36	Female	18
7	66	Male	16.5	Right	>10	25	69	Male	13
8	24	Female	14	Right	3	26	25	Female	16
9	57	Male	20	Right	2	24	54	Male	13
10	38	Female	18	Right	2	24	41	Female	15
M	47.8		16.4			26	48.7		14.6
SD	±16.97		±2.2			±3.9	±16.0		±3.5

Note. Education = years of education; Hand= handedness; Episodes= number of major depressive episodes; MADRS = Montgomery Åsberg Depression Rating Scale at baseline; *M* = mean; *SD* = standard deviation.

Table 2
Results for the different subjects in RCFT/TCFT (Rey´s Complex Figure Test, Taylor´s Complex Figure Test), Verbal fluency letter and category production, TMT A and B (Trailmaking Test) and WAIS-III (Wechsler Adult Intelligence Scale, version III)

	Controls		Patients	
	Baseline	Follow-up	Baseline	Follow-up
RCFT/TCFT 1	20.1 (7.8)$_{7}^{8}$	24.5 (3.2)$_{6}^{6}$	22.4 (7.2)$_{10}^{10}$	26.7 (6.1)$_{7}^{7}$
RCFT/TCFT 2	17.4 (6.6)$_{9}^{9}$	24.1 (4.3)$_{6}^{6}$	21.4 (8.5)$_{10}^{10}$	27.7 (5.2)$_{7}^{7}$
Letter production	33.9 (9.9)$_{9}^{9}$	38.8 (13.6)$_{6}^{6}$	46.4 (15.5)$_{10}^{10}$	55.6 (18.2)$_{7}^{7}$
Category production	43.2 (12.0)$_{9}^{9}$	54.5 (6.9)$_{6}^{6}$	50.8 (13.4)$_{10}^{10}$	61.3 (13.9)$_{7}^{7}$
TMT A	36.6 (12.0)$_{9}^{9}$	35.2 (12.6)$_{6}^{6}$	36.2 (11.0)$_{9}^{9}$	29.0 (13.2)$_{7}^{7}$
TMT B	93.1 (29.6)	66.5 (19.8)$_{8}^{8}$	75.1 (29.2)	61.1 (31.0)$_{7}^{7}$
WAIS-III	-	46.5 (9.4)	-	49.0 (6.8)

Note. RCFT (Rey´s complex figure test) at baseline and TCFT (Taylor´s complex figure test) at follow-up; superscript= number of participants in each test (max=10).

Table 3
Mean [^{11}C]AZ10419369 binding

	Controls BP_{ND} ±SD	Patients BP_{ND} ±SD (PET1)	Patients BP_{ND} ±SD (PET2)	Change in BP_{ND} ((PET2-PET1)/PET2)
OFC	1.08 ± 0.16	0.99 ± 0.36	0.93 ± 0.23	-0.05 ± 0.17
ACC	1.03 ± 0.25	0.80 ± 0.27	0.81 ± 0.18	0.01 ± 0.21
SPC	0.90 ± 0.11	0.71 ± 0.24	0.74 ± 0.19	0.05 ± 0.17
Ventral striatum	2.03 ± 0.40	1.79 ± 0.43	1.71 ± 0.31	-0.05 ± 0.20
Amygdala	0.91 ± 0.20	0.81 ± 0.38	0.73 ± 0.26	-0.15 ± 0.47
Hippocampus	0.33 ± 0.12	0.26 ± 0.12	0.21 ± 0.10	-0.31 ± 0.53
DBS	0.45 ± 0.28	0.56 ± 0.25	0.38 ± 0.20	-0.76 ± 1.02

Note. BP_{ND} = binding potential; SD= standard deviation; PET= positron emission tomography; OFC=orbitofrontal cortex; ACC=anterior cingulate cortex; SPC=subgenual prefrontal cortex; DBS=dorsal brainstem.

Table 4
Correlations (*r*) between the difference in cognitive test performance and difference in BP_{ND} in the patient group

	ΔTCFT/RCFT, delayed recall *r* (*p*)	ΔTCFT/RCFT, delayed recognition *r* (*p*)	ΔLetter production *r* (*p*)	ΔCategory production *r* (*p*)	ΔTMT A *r* (*p*)	ΔTMT B *r* (*p*)
ΔOFC	0.40 (0.38)	0.28 (0.54)	0.53 (0.22)	0.46 (0.30)	-0.19 (0.69)	0.53 (0.28)
ΔACC	0.31 (0.50)	0.23 (0.63)	0.37 (0.42)	0.26 (0.57)	-0.60 (0.15)	0.40 (0.44)
ΔSPC	-0.05 (0.91)	-0.14 (0.77)	0.02 (0.97)	0.24 (0.61)	-0.13 (0.78)	0.15 (0.78)
ΔVST	0.48 (0.28)	0.40 (0.37)	0.79 (0.03)*	0.50 (0.26)	-0.28 (0.55)	0.38 (0.46)
ΔAMY	0.74 (0.06)	0.61 (0.15)	0.40 (0.37)	0.76 (0.05) *	0.33 (0.47)	0.87 (0.02)*
ΔHIP	0.58 (0.17)	0.45 (0.31)	0.24 (0.60)	0.42 (0.35)	0.10 (0.83)	0.89 (0.02)*
ΔDBS	0.44 (0.32)	0.24 (0.60)	0.19 (0.69)	0.36 (0.43)	-0.04 (0.93)	0.85 (0.03)*

Note. RCFT=Rey´s Complex Figure Test; TCFT=Taylor´s Complex Figure Test; TMT A= Trailmaking test A; TMT B= Trailmaking test B; ACC=anterior cingulate cortex; OFC=orbitofrontal cortex; SPC=subgenual prefrontal cortex; VST= ventral striatum; DBS=dorsal brainstem; AMY=amygdala; HIP=hippocampus; *= $p<0.05$.

Supplementary table

Pearson´s correlations (r_{xy}) between cognitive performance and 5-HT1BR binding using the radioligand [^{11}C]AZ10419369 (BP_{ND}).

	RCFT/TCFT 1 Delayed recall			RCFT/TCFT 2 Delayed recognition			Verbal Fluency Letter production			Verbal Fluency Category production			TMT A			TMT B			WAIS-III	
	Baseline (r_{xy})		Follow-up (r_{xy})	Baseline (r_{xy})		Follow-up (r_{xy})	Baseline (r_{xy})		Follow-up (r_{xy})	Baseline (r_{xy})		Follow-up (r_{xy})	Baseline (r_{xy})		Follow-up (r_{xy})	Baseline (r_{xy})		Follow-up (r_{xy})	Follow-up (r_{xy})	
	P	C	P	P	C	P	P	C	P	P	C	P	P	C	P	P	C	P	P	C
OFC	0.58†	0.89**	0.13	0.62†	0.96***	0.16	-0.36	-0.46	-0.48	-0.07	-0.02	-0.07	-0.11	-0.39	0.05	-0.25	-0.26	-0.30	-0.33	0.20
ACC	0.56†	0.62	0.07	0.62†	0.69†	0.22	-0.19	-0.47	0.39	-0.01	-0.15	0.62	-0.03	-0.29	-0.54	-0.26	-0.33	-0.53	-0.07	-0.10
SPC	0.58	0.58	-0.09	0.43	0.42	-0.04	-0.19	0.16	-0.19	0.06	-0.00	0.30	0.08	-0.56	-0.38	-0.11	-0.05	-0.45	-0.00	0.58
AMY	0.65*	0.81*	0.17	0.66*	0.73†	0.22	-0.27	-0.23	-0.45	0.05	0.01	-0.28	-0.17	-0.07	0.23	-0.25	0.16	-0.20	-0.66	0.38
HIP	0.54	0.38	-0.15	0.57†	0.23	-0.12	-0.34	-0.12	-0.52	-0.09	0.06	-0.48	-0.20	0.35	0.25	-0.17	0.26	0.06	-0.42	-0.18
VST	0.69*	0.63†	0.41	0.71*	0.20	0.54	-0.26	-0.17	0.28	-0.10	-0.53	0.21	-0.33	0.31	-0.08	-0.31	0.64†	-0.46	-0.68†	0.20
DBS	0.69*	0.57	0.37	0.74*	0.83*	0.45	-0.17	0.02	-0.36	-0.05	0.62†	-0.00	-0.33	-0.53	0.16	-0.36	-0.44	-0.27	-0.44	0.20

Note. RCFT=Rey´s Complex Figure Test, delayed recall and delayed recognition; TCFT=Taylor´s Complex Figure Test, delayed recall and delayed recognition; TMT A= Trailmaking test A; TMT B= Trailmaking test B; WAIS-III=Wechsler´s Adult Intelligence Scale, version III; P=patient group; C=control group; OFC=orbitofrontal cortex; ACC=anterior cingulate cortex; SPC=subgenual prefrontal cortex; AMY=amygdala; HIP=hippocampus; VST=ventral striatum; DBS=dorsal brainstem; †=marginally significant; *< 0.05; **<0.001.

Figure 1. Scatter plot illustrating the association between the relative difference in letter production and binding potential (BP_{ND}) in ventral striatum.

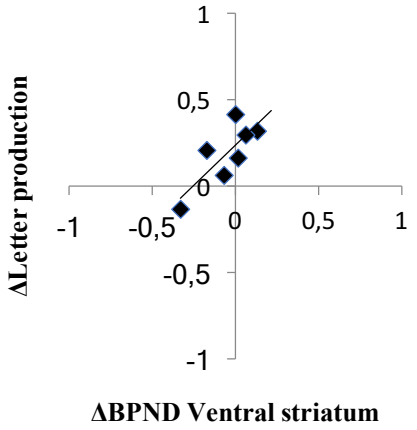

Figure 2. Scatter plot illustrating the association between relative difference in category production and binding potential (BP_{ND}) in amygdala.

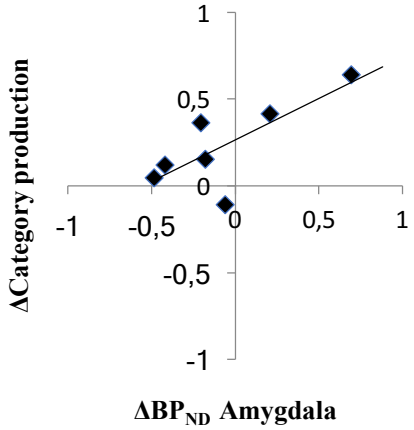

Figure 3. Scatter plot illustrating the association between relative difference in Trailmaking Test B (TMT B) performance and binding potential (BP_{ND}) in dorsal brainstem (DBS), amygdala and hippocampus.