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

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

4  
5 **Article type** Full Length Article

6  
7 **Abstract**

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

23  
24 **Keywords** Key words: 5-HT1BR; Depression; Internet-based CBT; Neuroimaging;  
25 Serotonin

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## 40 **1. Introduction**

41 Major depressive disorder (MDD) has a lifetime prevalence of 11-15 % (Bromet et al.,  
42 2011) and is the leading cause of disability worldwide (World Health Organization, 2017). It is a  
43 clinically heterogeneous disease of variable course in which the core symptoms, low mood and  
44 loss of interest, are related to emotional dysregulation. Recent research has demonstrated that also  
45 cognitive impairments play an important role in the symptomatology of MDD (Rock et al., 2014;  
46 Trivedi and Greer, 2014). These include reversible dysfunctions that largely normalize after a  
47 major depressive episode, that is, visuospatial short term memory function (Behnken et al.,  
48 2010), and persistent cognitive impairments remaining after remission, such as attention and  
49 executive functions (Rock et al., 2014; Årdal and Hammar, 2011). In a meta-analysis  
50 investigating executive function in 375 depressed patients and 481 control subjects, patients were  
51 found to perform significantly worse in tasks measuring semantic verbal fluency, cognitive  
52 flexibility and impulse inhibition (Wagner et al., 2012). Clinically significant impairments in  
53 several cognitive domains including psychomotor speed, attention, visual learning and memory,  
54 and executive functions have repeatedly been shown to be associated with MDD (Gallagher et  
55 al., 2007; Marazziti et al., 2010; Trivedi and Greer, 2014).

56 As the biological underpinning of MDD is largely unknown, so are the biological  
57 mechanisms mediating the cognitive deficits in MDD. Of the various hypotheses for MDD, the  
58 monoamine deficiency hypothesis is the most investigated (Aguirell, 1981; Coppen, 1967). The  
59 monoaminergic hypothesis is mainly based on observations of clinical effects of antidepressant  
60 drugs. The currently most widely used pharmacological treatment for MDD is selective serotonin  
61 reuptake inhibitors (SSRIs), which inhibit the serotonin transporter and modify serotonin  
62 concentration in the synaptic cleft (Lundberg et al., 2007; Nord et al., 2013; Romero et al., 1996).  
63 Additional support for an association between serotonin and depression comes from tryptophan  
64 depletion studies showing that acute tryptophan depletion results in increased depressive  
65 symptoms in remitted MDD patients and subjects with a family history of MDD (Ruhé et al.,  
66 2007).

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

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

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

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

100

## 101 **2. Material and methods**

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

106

### 107 *2.1. Recruitment of patients*

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

123

### 124 *2.2. Study design*

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

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

138

### 139 *2.2.1. Psychological treatment*

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

147

### 148 *2.3. Assessment of cognitive performance*

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

158

#### 159 *2.4. Image acquisition and analysis*

160 All subjects underwent MRI; Signa 1.5T or 3.0T, GE Healthcare, for exclusion of brain  
161 pathology and co-registration with PET data. An individual head fixation system was used during  
162 PET measurements (Bergström et al., 1981). Each patient was examined twice with PET; ECAT  
163 High Resolution Research Tomograph (HRRT, Siemens Molecular Imaging) and the radioligand  
164 [<sup>11</sup>C]AZ10419369 (injected radioactivity: 385.7 ± 30.9 MBq). Brain radioactivity in each PET  
165 examination was measured during 93 minutes with a frame sequences ranging from 20 seconds to  
166 six minutes. SPM5 (Statistical Parametric Mapping, Wellcome Trust Centre for Neuroimaging,  
167 U.K.) was used to co-register T1-weighted (T1-w) MRI images to PET images and to segment  
168 MRI images. Regions of interest (ROI) were defined according to previous studies (Tiger et al.,  
169 2016, 2014) and chosen based on previous literature showing abnormal serotonin marker  
170 densities in MDD (Drevets, 2000; Murrough et al., 2011; Savitz and Drevets, 2013): orbitofrontal  
171 cortex (OFC), anterior cingulate cortex (ACC), subgenual prefrontal cortex (SPC), amygdala,  
172 hippocampus (both dorsal and ventral sub regions), ventral striatum and dorsal brainstem (DBS),

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

179

## 180 2.5. Statistics

181 Paired samples *t*-tests were applied to compare the results of cognitive performance, and 5-  
182 HT1BR binding between the two groups and pre-/post- treatment. Effects of diagnostic group and  
183 test occasion on cognitive performance were analyzed by a mixed effects modelling approach for  
184 repeated measures, as this allows accommodating missing data and the integration of time-  
185 varying factors. Group and time were considered as fixed effects in the model. Cognitive  
186 performance and 5-HT1BR binding was related using Pearson's correlation coefficients. For  
187 correlations found to be significant in the initial analyses, hierarchical multiple regression models  
188 were applied for each group and time point of examination by using each significant cognitive  
189 test result as a dependent variable and age, educational level as well as  $BP_{ND}$  for each significant  
190 ROI as predictors. In order to explore the relationship between differences in cognitive  
191 performance and differences in 5-HT1BR binding, the relative change in cognitive performance  
192 and 5-HT1BR binding between baseline and follow-up (cognitive performance follow-up –  
193 cognitive performance baseline)/cognitive performance baseline= $\Delta CP$ ; ( $BP_{ND}$  follow-up –  $BP_{ND}$   
194 baseline)/ $BP_{ND}$  baseline= $\Delta BP_{ND}$ ) as well as between differences in cognitive performance ( $\Delta CP$ )  
195 and clinical change using MADRS (MADRS score follow-up – MADRS score baseline/MADRS  
196 score baseline= $\Delta MADRS$ ) 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 ( $p>0.05$ ).

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

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

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

237

### 238 3.3. Group differences in cognitive performance at baseline

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

241

### 242 3.4. Group differences in cognitive performance at follow-up

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

246

### 247 *3.5. Effect of time and group on cognitive performance*

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

253

### 254 *3.6. Difference in cognitive performance and 5-HT1BR binding before and after treatment*

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

263

### 264 *3.7. Difference in cognitive performance and clinical change before and after treatment*

265           Within the patient group, Pearson's correlation coefficient revealed no significant  
266 correlations ( $p<0.05$ ) between difference in cognitive performance ( $\Delta$ CP) and difference in  
267 clinical change ( $\Delta$ MADRS) between baseline and follow-up.

268

#### 269 **4. Discussion**

270           Previous research in animal models, healthy volunteers and MDD patients suggests a role  
271 for 5-HT1BR in major depressive disorder and cognition. For instance, studies show 5-HT1BR  
272 binding reduction in DBS (Tiger et al., 2014), ACC, SGPFC and hippocampus (Tiger et al.,  
273 2016) as well as in ventral striatum/ventral pallidum (Murrough et al., 2011). In this exploratory  
274 study, the relation between cognitive performance in tests sensitive to MDD and 5-HT1BR  
275 binding in brain regions suggested to be involved in the pathophysiology of MDD have been  
276 investigated.

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

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

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

298 TMT B measures spatial navigation, sustained attention, psychomotor speed and  
299 executive function (Gould et al., 2007; Kortte et al., 2002; Porter et al., 2003; Snyder, 2013),  
300 domains known to be impaired in MDD (Rock et al., 2014; Wagner et al., 2012). Serotonin has  
301 been suggested to be mediating these symptoms, as for instance improvement in psychomotor  
302 speed is a known effect from successful treatment of MDD using SSRIs (Blier et al., 1990;  
303 Rosenblat et al., 2015). The DBS encloses a major part of the rostral raphe nuclei where the  
304 largest group of serotonergic neurons within CNS are situated, making it a key region for  
305 regulation of serotonin transmission, that is, decreased 5-HT1BR binding in DBS may reflect  
306 globally increased serotonergic activity affecting cognitive functions measured with TMT B.  
307 Regarding the amygdala, it has been shown in meta-analyses of fMRI research that the amygdala  
308 of patients with affective disorder is more activated during a task measuring sustained attention  
309 compared to controls (Sepede et al., 2014). Rumination, an activity negatively associated with  
310 sustained attention, has been shown to be positively associated to increased amygdala reactivity  
311 as well as abnormal metabolic activity in the hippocampus in MDD subjects (Mandell et al.,  
312 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

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

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

346

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352

#### 353 **Declaration of interest**

354 No conflict of interest for any of the authors.

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531

Table 1

Patient and matched control subject characteristics

Nr	Patients						Matched controls		
	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
<i>M</i>	47.8		16.4			26	48.7		14.6
<i>SD</i>	±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) <sub>8</sub>	24.5 (3.2) <sub>6</sub>	22.4 (7.2) <sub>10</sub>	26.7 (6.1) <sub>7</sub>
RCFT/TCFT 2	17.4 (6.6) <sub>9</sub>	24.1 (4.3) <sub>6</sub>	21.4 (8.5) <sub>10</sub>	27.7 (5.2) <sub>7</sub>
Letter production	33.9 (9.9) <sub>9</sub>	38.8 (13.6) <sub>6</sub>	46.4 (15.5) <sub>10</sub>	55.6 (18.2) <sub>7</sub>
Category production	43.2 (12.0) <sub>9</sub>	54.5 (6.9) <sub>6</sub>	50.8 (13.4) <sub>10</sub>	61.3 (13.9) <sub>7</sub>
TMT A	36.6 (12.0) <sub>9</sub>	35.2 (12.6) <sub>6</sub>	36.2 (11.0) <sub>9</sub>	29.0 (13.2) <sub>7</sub>
TMT B	93.1 (29.6)	66.5 (19.8) <sub>8</sub>	75.1 (29.2)	61.1 (31.0) <sub>7</sub>
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 [<sup>11</sup>C]AZ10419369 binding

	Controls BP <sub>ND</sub> ±SD	Patients BP <sub>ND</sub> ±SD (PET1)	Patients BP <sub>ND</sub> ±SD (PET2)	Change in BP <sub>ND</sub> ((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<sub>ND</sub> = 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<sub>ND</sub> in the patient group

	ΔTCFT/RCFT, delayed recall <i>r</i> ( <i>p</i> )	ΔTCFT/RCFT, delayed recognition <i>r</i> ( <i>p</i> )	ΔLetter production <i>r</i> ( <i>p</i> )	ΔCategory production <i>r</i> ( <i>p</i> )	ΔTMT A <i>r</i> ( <i>p</i> )	ΔTMT B <i>r</i> ( <i>p</i> )
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 [ $^{11}\text{C}$ ]AZ10419369 ( $\text{BP}_{\text{ND}}$ ).

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

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.

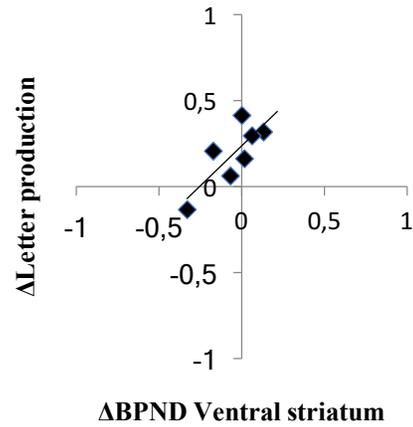


Figure 2. Scatter plot illustrating the association between relative difference in category production and binding potential ( $BP_{ND}$ ) in amygdala.

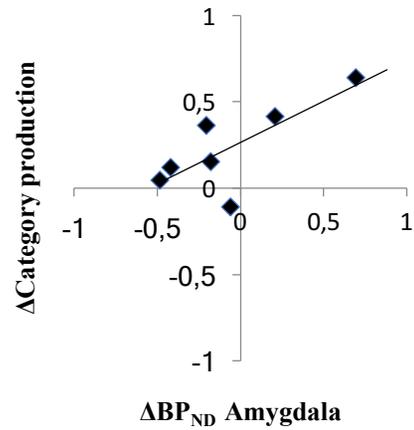


Figure 3. Scatter plot illustrating the association between relative difference in Trailmaking Test B (TMT B) performance and binding potential ( $BP_{ND}$ ) in dorsal brainstem (DBS), amygdala and hippocampus.

