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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 (Agurell, 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_{1A} 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 [¹¹C]AZ10419369 correlations have been shown between [¹¹C]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 [¹¹C]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 [¹¹C]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 (± 3 years (± 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 ± 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 ± 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 [¹¹C]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= ΔCP ; (BP_{ND} follow-up – BP_{ND}
194 baseline)/ BP_{ND} baseline= ΔBP_{ND}) as well as between differences in cognitive performance (ΔCP)
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 (ΔCP
257 and ΔBP_{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 (Δ CP) and difference in
267 clinical change (Δ 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) ₈	24.5 (3.2) ₆	22.4 (7.2) ₁₀	26.7 (6.1) ₇
RCFT/TCFT 2	17.4 (6.6) ₉	24.1 (4.3) ₆	21.4 (8.5) ₁₀	27.7 (5.2) ₇
Letter production	33.9 (9.9) ₉	38.8 (13.6) ₆	46.4 (15.5) ₁₀	55.6 (18.2) ₇
Category production	43.2 (12.0) ₉	54.5 (6.9) ₆	50.8 (13.4) ₁₀	61.3 (13.9) ₇
TMT A	36.6 (12.0) ₉	35.2 (12.6) ₆	36.2 (11.0) ₉	29.0 (13.2) ₇
TMT B	93.1 (29.6)	66.5 (19.8) ₈	75.1 (29.2)	61.1 (31.0) 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 [¹¹C]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 <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}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 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.

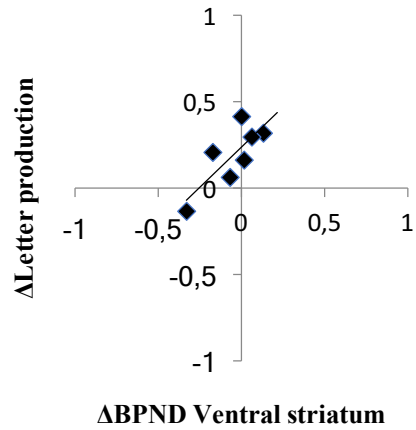


Figure 2. Scatter plot illustrating the association between relative difference in category production and binding potential (BP_{ND}) in amygdala.

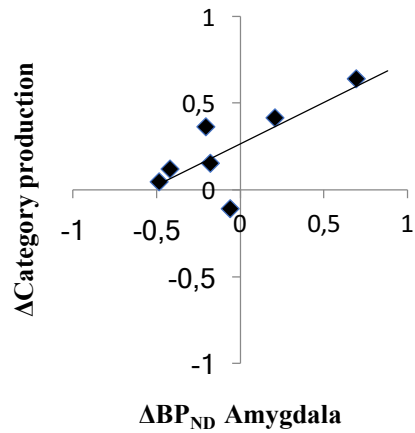


Figure 3. Scatter plot illustrating the association between relative difference in Trailmaking Test B (TMT B) performance and binding potential (BP_{ND}) in dorsal brainstem (DBS), amygdala and hippocampus.

