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ARTICLE

Metabotropic glutamate receptor 5 binding in patients with obsessive-compulsive disorder

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Abstract

Obsessive-compulsive disorder (OCD) is a disabling, mostly chronic, psychiatric condition with significant social and economic impairments and is a major public health issue. However, numerous patients are resistant to currently available pharmacological and psychological interventions. Given that recent animal studies and magnetic resonance spectroscopy research points to glutamate dysfunction in OCD, we investigated the metabotropic glutamate receptor 5 (mGluR5) in patients with OCD and healthy controls. We determined mGluR5 distribution volume ratio (DVR) in the brain of ten patients with OCD and ten healthy controls by using [11C]ABP688 positron-emission tomography. As a clinical measure of OCD severity, the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) was employed. We found no significant global difference in mGluR5 DVR between patients with OCD and healthy controls. We did, however, observe significant positive correlations between the Y-BOCS obsession sub-score and mGluR5 DVR in the cortico-striatal-thalamo-cortical brain circuit, including regions of the amygdala, anterior cingulate cortex, and medial orbitofrontal cortex (Spearman's ρ's $\geqslant$ =0.68, p<0.05). These results suggest that obsessions in particular might have an underlying glutamatergic pathology related to mGluR5. The research indicates that the development of metabotropic glutamate agents would be useful as a new treatment for OCD.

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Introduction

Individuals suffering from obsessive-compulsive disorder (OCD) display recurrent, intrusive thoughts (obsessions) and/or repetitive behaviour that the individual feels driven to perform (compulsions) (Hasler et al., 2005, 2007). Patients recognize that these thoughts and behaviours are excessive and unreasonable, and attempt to suppress them. The obsessions and compulsions cause significant impairment in social and occupational functioning (Fontenelle and Hasler, 2007), leading to health cost burdens and personal patient tragedies. According to the World Health Organization, OCD is among the ten most disabling medical conditions (Murray and Lopez, 1996) with a life-time prevalence rate of 1.9–2.5% (Stein et al., 2000; Nestadt et al., 2010).

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Advances in the pharmacological treatment of OCD have increased since the 1980s, when serotonin reuptake inhibitors (SRI) were introduced as an intervention method, successfully reducing the symptoms of OCD in some patients (Hoehn-Saric et al., 2000). The success rate of SRI treatments for OCD, even when combined with psychological therapies such as cognitive behavioural therapy, was only 40–60% (Nestadt et al., 2010). Recently, research interest has shifted toward examining the role of glutamate in OCD (Bhattacharyya and Chakraborty, 2007; Riaza Bermudo-Soriano et al., 2012; Wu et al., 2012). Magnetic resonance spectroscopy (MRS) imaging studies have found reduced glutamate concentrations in portions of the cortico-striatal-thalamo-cortical brain circuit, such as the amygdala and orbitofrontal cortex, in adults and children with OCD (Bhattacharyya and Chakraborty, 2007). In a recent review (Brennan et al., 2012) compared the results of 14 MRS studies investigating a glutamate-related chemical in patients with OCD and healthy controls. The authors reported that a majority of studies found decreased glutamate metabolites in the anterior cingulate cortex (ACC) of

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adults and increased metabolites in the caudate nucleus of children. Further evidence for the prominent role of glutamate in OCD comes from preclinical studies of pharmaceuticals that act on metabotropic glutamate mGluR5 receptors. These antagonists have consistently been reported to have anxiolytic effects in animal experiments, and more specific effects on OCD-like behaviour in animal models (Pittenger et al., 2006; Bhattacharyya and Chakraborty, 2007; Riaza Bermudo-Soriano et al., 2012). In addition, there are recent reports demonstrating efficacy of mGluR5 antagonists in preclinical tests related to OCD (Spooren et al., 2000; Mehta et al., 2011).

Using positron emission tomography (PET) with the successfully developed radiolabeled mGluR5 antagonist ([^{11}C]ABP688) (Ametamey et al., 2007), which binds with high selectivity to an allosteric site, we could measure mGluR5 availability in healthy subjects and patients with OCD. On the basis of previous theories suggesting the involvement of the cortico-striatal-thalamo-cortical brain circuit glutamate concentration in OCD (Saxena et al., 1998; Wu et al., 2012), we predicted changes in mGluR5 distribution volume ratio within regions of interest (ROIs) that are part of this brain circuit, such as the orbitofrontal cortex, ACC and subcortical regions such as the amygdala.

Method

Subjects

Participants were recruited via local newspaper advertisements and posters at Zurich University hospital, and were assessed during a screening visit to the outpatient psychiatry clinic of Zurich University hospital. Inclusion criterion for the group of patients with OCD was the presence of obsessions and compulsions for at least 1 h every day. To exclude individuals with additional current psychiatric illnesses, all subjects were assessed with an unstructured clinical interview by a psychiatrist, and the Structured Clinical Interview for the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (First et al., 2001). The clinical evaluation also included a physical examination, laboratory tests, and in some cases electrocardiography to ensure that patients were eligible for the PET scan. Clinical measures included the Yale-Brown Obsessive Compulsive Scale (Y-BOCS) (Goodman et al., 1989), Beck Anxiety Inventory (BAI) (Beck et al., 1988) and the Beck Depression Inventory (BDI) (Beck et al., 1961).

Exclusion criteria included additional current psychiatric, neurological, or medical disorders, pregnancy, breastfeeding, history of psychosis, manic episodes, substance dependence, nicotine consumption and autism. Healthy controls were excluded if any current Axis I mental illness or any counter-indication for PET scan was determined. Magnetic resonance imaging was performed on each subject and assessed by a radiologist to exclude any structural brain pathology.

Subjects were enrolled in the study after they received a full explanation of the study purpose and procedures, and after written consent was obtained as approved by the local ethics committee (Kantonale Ethikkommission Zurich).

Positron emission tomography

A bolus/infusion protocol (Carson et al., 1993) that we previously evaluated for PET with [^{11}C]ABP688 (Burger et al., 2010) was applied. This protocol allows reliable measurement of the relative distribution volume and reduction of potential bias due to arterial blood sampling needed for absolute quantification. Studies have demonstrated that equilibrium between the tracer in tissue and blood is achieved 40 min after the start of radioligand infusion (Burger et al., 2010). Each patient's dynamic uptake curve was checked for suitability. Catheters were placed in the right antecubital vein for tracer injection prior to scanning. Subjects were scanned using [^{11}C]ABP688 and a whole-body PET (Discovery VCT; GE Healthcare, US) in three-dimensional mode with an axial field of view of 14.6 cm and an in-plane resolution of 7.0 mm. For attenuation correction, low-dose computed tomography was acquired before tracer injection. A total of 600–800 MBq of [^{11}C]ABP688 in a 50 ml volume was administered using an infusion pump (half was given as a bolus over 2 min and the other half was infused over the next 58 min). Image acquisition and reconstruction was performed as described earlier (Treyer et al., 2007). In brief, the emission scan, which consisted of 20 frames (10 frames of 60 s followed by 10 frames of 300 s, leading to a total duration of 60 min per acquisition), was initiated at the start of the bolus injection. Transaxial images were reconstructed to a 128 × 128 matrix with 35 slices of 2.34 × 2.34 × 3.27 mm voxel size using filtered back-projection. To determine that equilibrium was reached in each subject, we analysed the tissue time-activity curve in a cingular (high receptor density) and a grey matter cerebellar (low receptor density) region. We found that the activity reached equilibrium at 30 min. As the measure of receptor availability, the ratio of tissue activity divided by the cerebellar activity at equilibrium (C_T/C_{cer} at 45–60 min) was chosen. At equilibrium, C_T/C_{cer} is equal to the ratio of the distribution volumes of the tracer in target and reference tissue, $(C_T/C_{cer})_{eq}=V_T/V_{ND}$, where V_{ND} is the distribution volume of the non-displaceable compartment (Treyer et al., 2007) — in our case, the cerebellum. V_T/V_{ND} is referred to as the distribution volume ratio (DVR). It can be further demonstrated that the DVR equals $BP_{ND}+1$, where BP_{ND} is the binding potential in the target tissue, which is often used as measure for receptor density divided by affinity (Innis et al., 2007).

Statistical analysis

Analyses were conducted using PMOD (Version 3.0; PMOD Technologies, Switzerland, www.pmod.com).

Table 1. Clinical characteristics of the two groups

Clinical characteristic	OCD (n=10)	Healthy subjects (n=10)
Gender (f/m)	9/1	7/3
Age (yr)	36.40 (8.59)	36.10 (8.06)
Duration of illness (yr)	11.60 (6.96)	–
Yale-Brown Obsessive-Compulsive Scale (Y-BOCS)		
Y-BOCS-Total score	26.00 (5.35)	
Y-BOCS-Obsessions score	13.00 (2.94)	
Y-BOCS-Compulsions score	13.10 (3.07)	
OCD symptom clusters*	Contamination/cleaning n=5	–
	Harm/checking n=3	
	Symmetry/ordering n=5	
	Hoarding n=0	
	Miscellaneous n=8	
Beck Depression Inventory score	9.70 (4.57)	2.10 (2.08)
Beck Anxiety Inventory score	14.40 (6.15)	1.60 (1.08)
Past psychiatric history*	Major depressive disorder n=7	Major depression episode n=2
	Social phobia n=4	
Medication at time of study*	Escitalopram n=1	–
	Paroxetine n=1	
	Sertraline n=1	
	Fluctine n=1	
	Clomipramine with an adjunct Risperidone n=1	
Highest educational qualification*	High school completed n=4	High school completed n=2
	College completed n=6	College completed n=7
	University completed n=0	University completed n=1

The data presented are Mean (S.D.), unless indicated otherwise.
* n refers to the number of participants within this category.

First, DVR images were transformed to a common space, the Montreal Neurological Institute template. Pre-defined grey matter ROIs were applied to the normalized DVR PET images. The ROIs included 24 regions: 4 cortical (frontal, parietal, temporal, and occipital), 2 regions within the cingulate gyrus (anterior and posterior), 3 regions in the prosencephalon (caudate, putamen, and thalamus) and 3 regions in the limbic system (medial orbitofrontal cortex, amygdala, and medial temporal lobe). Additionally, we calculated the average grey matter mGluR5 DVR using a grey matter mask with a pixel value cut-off of 12. Two-sample two-tailed t-tests were used to test the differences in mGluR5 DVR between the groups with and without Bonferroni correction. Spearman correlations were used to assess associations between continuous variables and mGluR5 DVR within each group.

Results

The clinical characteristics of ten OCD and ten age- and gender-matched healthy subjects are shown in Table 1. Age did not differ across the groups (t_{18}=0.08, p=0.94), and there was no significant age difference between male and female subjects in the total sample (t_{18}=−0.61, p=0.55). Additionally, we observed no difference in highest educational qualification between the groups (all p's> 0.20). Both groups differed with respect to the BDI (t_{18}= 4.79, p<0.001) and BAI scores (t_{18}=6.48, p<0.001) (See Table 1). Seven patients with OCD had a history, but no present episode, of major depressive disorder (MDD) and two had a history of social phobia. Among the controls, two individuals had a past major depressive episode. The mean [11C]ABP688 activity administered did not differ significantly between OCD and healthy subjects (729±71 and 740±34 MBq). Overall, we observed no significant difference in mGluR5 DVR between OCD and healthy subjects in any ROI examined, with and without correction for multiple tests. Figure 1 shows the distribution of all DVRs over all regions in both groups revealing high overlap between groups. However, among patients with OCD, Y-BOCS total score and mGluR5 DVR were positively correlated in the right medial temporal (ρ=0.78, p=0.01), right medial orbitofrontal cortex (ρ=0.83, p=0.03) and right parietal cortex (ρ=0.66, p= 0.04), as well as in the temporal lobes (right: ρ=0.87, p= 0.01; left: ρ=0.87, p=0.01). Interestingly, the YBOCS compulsions sub-score did not correlate with mGluR5 DVR in any ROI. However, the YBOCS obsession sub-score correlated positively with the average grey matter mGluR5 DVR (ρ=0.72, p=0.02 (0.48 Bonf)). Specifically, the obsession sub-score correlated with mGluR5 in the ACC (ρ=0.68, p=0.03 (0.72 Bonf)), right amygdala (ρ=0.74,

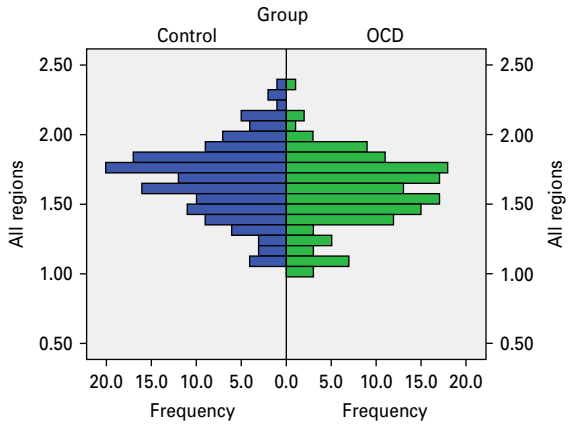

Fig. 1. Histogram of DVR in all regions over all subjects comparing both groups showing high overlap.

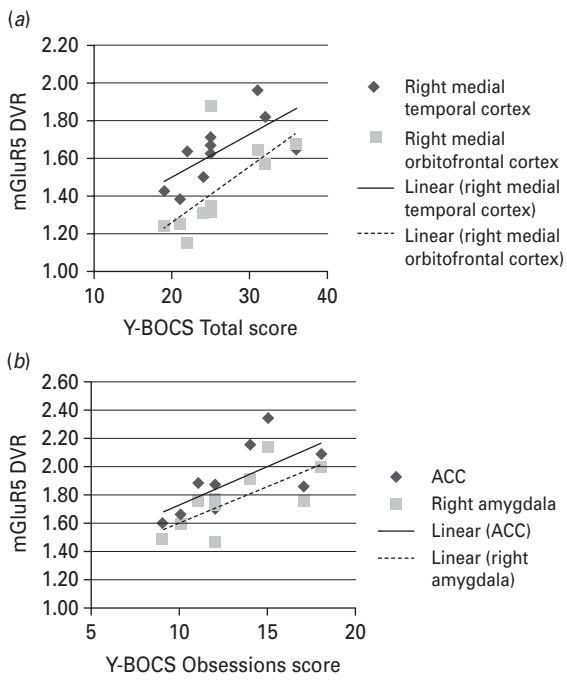

Fig. 2. (*a*) Correlation between Y-BOCS obsessions score and mGluR5 DVR in right medial temporal cortex and right medial orbitofrontal cortex. (*b*) Correlation between Y-BOCS obsessions score and mGluR5 DVR in ACC and amygdala.

p=0.02 (0.48 Bonf)), right frontal lobe (ρ=0.79, p=0.01 (0.245 Bonf)), medial temporal lobes (right: ρ=0.78, p=0.01 (0.245 Bonf); left: ρ=0.77, p=0.01 (0.245 Bonf)), medial orbitofrontal cortex (right: ρ=0.73, p=0.02 (0.48 Bonf); left: ρ=0.75, p=0.01 (0.245 Bonf)), parietal lobes (right: ρ=0.80, p=0.01 (0.245 Bonf); left: ρ=0.82, p=0.01 (0.245 Bonf)), and temporal lobes (right: ρ=0.88, p<0.01 (0.245 Bonf); left: ρ=0.85, p=0.02 (0.48 Bonf)). Results were the same when correlations were determined with Pearson correlation. Figure 2*a, b* displays the correlations between and Y-BOCS total score and mGluR5 DVR in right medial temporal cortex and right medial

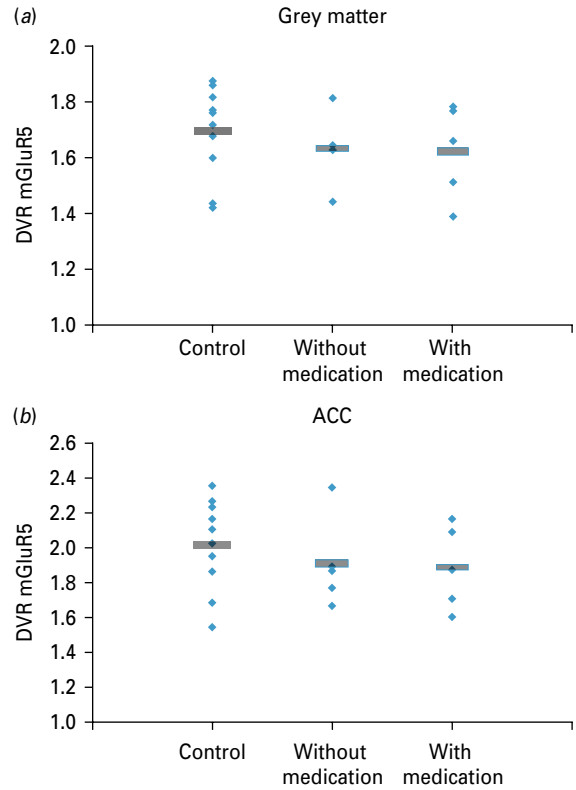

Fig. 3. (*a*) Scattergrams of mGluR5 binding of grey matter. Control, without medication and with medication group. (*b*) Scatter grams of mGluR5 binding of ACC. Control, without medication and with medication group.

orbitofrontal cortex (a) and Y-BOCS obsessions score and mGluR5 DVR in ACC and right amygdala (b). Figure 1 in the supplemental material shows that medication did not seem to have an effect on these correlations in this study. Comparing the slopes of the regressions with and without medication did also not reveal a significant difference (t=0.5, df=6). Controlling the correlation for medication the correlation is 0.716 with 2-tailed p=0.03, which is not much different from the result without controlling for medication: ρ=0.74, p=0.02. To display raw data variability Fig. 3*a, b* displays the values of grey matter and ACC in controls, OCD with and without medication. Figure 4 depicts mGluR5 DVR in OCD patients with and without obsessions.

In the healthy control group, BDI and BAI scores did not correlate with the mGluR5 DVR in any ROI. However, in the OCD group, the BAI score was positively correlated with the mGluR5 DVR in the right putamen (ρ=0.68, p=0.03 (0.245 Bonf)) and the BDI score was positively correlated with mGluR5 DVR in the right caudate (ρ=0.71, p=0.02 (0.245 Bonf)).

Discussion

In this PET study we investigated mGluR5 distribution volume ratio of ten adult patients with OCD compared

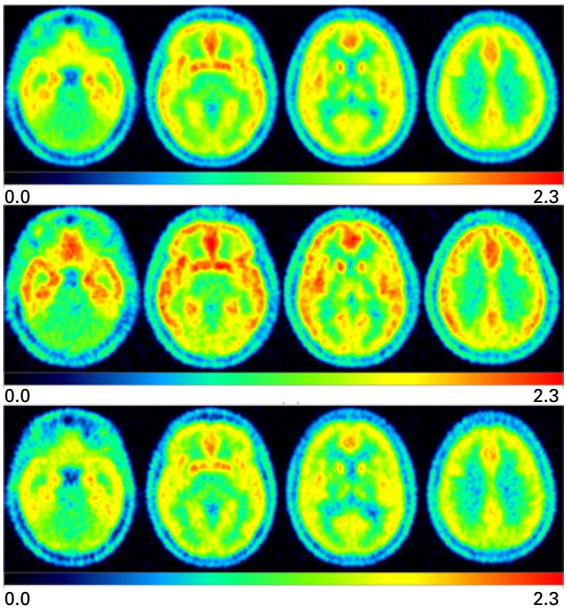

Fig. 4. mGluR5 DVR in OCD patients with and without obsessions. Figure depicts mGluR5 DVR in horizontal slices. Upper row: average mGluR5 binding in the 11 subjects with OCD. Middle and lower rows: subjects with OCD were divided by median split; middle row shows the 4 subjects with OCD with high Y-BOCS obsession scores (13–18), bottom row shows the 6 subjects with OCD with low Y-BOCS obsession scores (9–12).

to ten healthy controls. We did not find global differences between the two groups; however, we found significant positive correlations between the Y-BOCS obsession sub-score and the mGluR5 DVR in the ACC, right amygdala, right frontal cortex, grey matter, bilateral medial temporal cortex, bilateral medial orbitofrontal cortex, bilateral parietal lobe, left temporal lobe and right temporal lobe. The compulsions score was not correlated with mGluR5 DVR in any ROI.

Several factors may have contributed to the lack of significant differences in mGluR5 DVR between patients with OCD and controls. OCD patients had a higher load of depressive symptoms than control subjects. Given that depression has been related to global reductions in mGluR5 binding (Deschwanden et al., 2011b), this depression-related reduction might have counterbalanced the potential obsessive symptoms related increase in mGluR5 DVR, as seen within the OCD sample.

The correlation between mGluR5 DVR and the obsession sub-score confirms previous research using different methodologies, such as MRS or animal models, suggesting that glutamate plays an important role in the pathogenesis of OCD (Pittenger et al., 2006; Bhattacharyya and Chakraborty, 2007; Harvey and Shahid, 2012; Riaza Bermudo-Soriano et al., 2012). Furthermore, we found that the obsession score correlated with mGluR5 DVR in cortico-striatal-thalamo-cortical brain circuit, including regions of the amygdala, ACC and medial orbitofrontal cortex, confirming the role of this specific brain circuitry in OCD pathology. Indeed, we found changes in mGluR5 distribution volume ratio in key regions that were previously associated with abnormalities in OCD (Rosenberg and Keshavan, 1998; Szeszko et al., 2008). Using neuroimaging methods in patients with OCD and healthy controls, structural brain abnormalities have consistently been reported in those regions that we also determined to be significantly affected, such as the amygdala (Rosenberg and Keshavan, 1998), ACC (Szeszko et al., 2008) and orbitofrontal cortex (Rosenberg and Keshavan, 1998; Szeszko et al., 2008; van den Heuvel et al., 2009). This suggests that structural changes in brain anatomy might be associated with molecular changes in glutamate function and receptor distribution. Additionally, frontal deficits might be associated with deficits in executive function mechanisms (such as obtrusive thinking) involved in obsessions, while glutamatergic changes in limbic regions might be associated with fear/stress responses, which are commonly connected to obsessions.

We found correlations between mGluR5 distribution volume ratio and the obsessions, but not the compulsions sub-score (or overall), which might suggest that each has a distinguishable underlying pathophysiology. Obsessions involving stress, conflict and executive function problems can be associated with glutamatergic changes in key regions mediating such responses (i.e. the amygdala, ACC and orbitofrontal cortex (Rosenberg and Keshavan, 1998; Szeszko et al., 2008; van den Heuvel et al., 2009)), whereas compulsions might have a stronger motor component, potentially associated with changes in the cerebellum, that have very low mGluR5 binding.

Several studies (DeLorenzo et al., 2011; Sandiego et al., 2013; Wyckhuys et al., 2013) addressed the variability of [^{11}C]ABP688 binding. With regards to intra-subject variability's test and re-test studies have not shown significant effects, except one study, which had revealed an unexplained effect (Sandiego et al., 2013). The question of present PET study was to explore if there is a difference in metabotropic glutamate receptor 5 binding between healthy group and patients with OCD and we did not find a clear effect. Considering potential medication targeting directly or indirectly the mGluR5 system a further study analysing effects using this tracer would nevertheless make sense but would need a higher number of subjects to be enrolled to ensure better power for detecting intra-individual changes.

One limitation of the current research is the relatively small sample size. However, we recently determined reduced mGluR5 receptor density in smokers and depressed individuals by using a marginally larger number of participants (Deschwanden et al., 2011b; Akkus et al., 2013). Importantly, in the current BDI estimate only three patients had a score over eleven. Nevertheless, the effect of comorbidity was too small to find a difference

in tracer uptake between both groups. For test purposes we used BDI as covariate comparing the grey matter uptake between groups and did not find an interesting effect in any direction (univariate ANOVA without BDI: $F=0.914$, $p=0.352$, with BDI as covariate: corrected model $F=1.78$, $p=0.199$, for group effect $F=3.46$, $p=0.08$, with BAI as covariate: corrected model $F=1.164$, $p=0.336$, for group effect $F=2.302$ $p=0.148$).

A further limitation might be that some study patients took medications for OCD symptoms ($n=5$), which could have interfered with the results. This limitation may have increased the probability of type II errors with respect to differences between cases and controls. Since we did not find global changes in glutamate receptor density but found very specific ROI changes in our OCD sample that were correlated with obsessions but not compulsions, it is very unlikely that this specific finding could be attributed to medications as they would more likely produce non-specific global changes. Indeed, medication did not seem to have an effect on the correlations in this study (see Fig. 1 supplemental material). Also looking at data distribution between the different groups (control, OCD with and without medication) there seems no trend in the data visible potentially related to medication (see Fig. 3*a*, *b*). Finally, since some patients also reported having been diagnosed with depression in the past, one might suggest a potential confound here. However, we carefully selected patients who were currently free of any condition other than OCD. Additionally, in a recent study we found that depression was associated with a decrease rather than an increase in mGluR5 receptor density (Deschwanden et al., 2011b). Excluding the two control subjects with a past major depressive episode did not change the results of this study. Taken together, limitations of this research might be the relative small sample size and the comorbidity of some patients, therefore further research, for instance using a large sample of OCD patients receiving mGluR5-based treatment in a controlled clinical trial, would be helpful to confirm this initial finding.

We used a bolus-infusion technique and normalized the PET images to the cerebellar radioactivity concentration to avoid the need for potentially painful arterial cannulation. This reference tissue method was based on previous *in vivo* and *in vitro* evidence demonstrating that mGluR5 levels are extremely low in the cerebellum relative to the predefined ROIs in other brain areas (Elmenhorst et al., 2010). A recent study demonstrated that quantification of mGluR5 receptor with [^{18}F]FPEB using non-invasive modelling with the cerebellum as a reference region may be feasible (Barret et al., 2010). In support of this, recent *in vitro* and *in vivo* studies suggested negligible ABP688 binding in the cerebellum, and validated the use of the cerebellum as a reference region (Ametamey et al., 2007; Elmenhorst et al., 2010). In addition, in a recent post-mortem study, mGluR5 protein expression was not observed in the cerebellum (Deschwanden et al., 2011a). Previous studies on cerebellar mRNA expression have demonstrated both the presence (Malherbe et al., 2002) and absence (Daggett et al., 1995) of mGluR5 mRNA, or weak mRNA expression exclusively in Bergmann glia (Berthele et al., 1999). In summary, in all studies of cerebellar mGluR5 concentration that collected data from more than one subject (Patel et al., 2007) found negligible mGluR5 expression in the cerebellum, suggesting that the cerebellum can be used as a reference region.

Overall, our research suggests that glutamatergic transmission in cortico-striatal-thalamo-cortical brain circuits is related to obsessions—but not compulsions—in OCD. Recent pharmacological studies and preclinical animal studies have demonstrated promising anxiolytic effects of some glutamate-based antagonists (Pittenger et al., 2006; Harvey and Shahid, 2012; Riaza Bermudo-Soriano et al., 2012). Specifically, it has been suggested that compared to drugs acting on ionotropic glutamate receptors, antagonists acting on metabotropic glutamate receptors, such as the mGluR5, might be more specific and cause less unwanted effects than ionotropic agents (Pittenger et al., 2006; Harvey and Shahid, 2012; Riaza Bermudo-Soriano et al., 2012). Our research identifies that the development of metabotropic glutamate-based antagonists for OCD could offer a new treatment option for patients with OCD.

Supplementary material

For supplementary material accompanying this paper, visit http://dx.doi.org/10.1017/S1461145714000716.

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Statement of Interest

Funda Akkus, Sylvia Terbeck, Simon M. Ametamey, Michael Rufer, Valerie Treyer, Cyrill Burger, Anass Johayem, Alfred Buck and Gregor Hasler do not have a conflict of interest regarding the content of this article. Baltazar Gomez Mancilla and Judit Sovago are employees of Novartis Pharma AG (Basel, Switzerland) that is developing and testing drugs targeting the mGlu5 receptor. Cyrill Burger works for PMOD Technologies Ltd., Zurich who developed the imaging software used in this study.

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