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SHORT COMMUNICATION

Higher serotonin transporter availability in early-onset obsessive–compulsive disorder patients undergoing escitalopram treatment: A [^{11}C]DASB PET study

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Abstract

Objective: Early-onset obsessive–compulsive disorder (EOCD) and late-onset obsessive–compulsive disorder (LOCD) are distinct subtypes of obsessive–compulsive disorder (OCD). OCD patients are treated with serotonin reuptake inhibitors, but the difference in serotonin transporter (SERT) availability between medicated EOCD and LOCD is unexplored yet.

Methods: Six EOCD and 6 LOCD patients were enrolled. They underwent serial [^{11}C]DASB positron emission tomography scans during maintenance therapy with escitalopram, and their plasma concentration of escitalopram was measured simultaneously with the scan. Then, the drug-free binding potential of SERT was calculated by pharmacokinetic–pharmacodynamic modelling.

Results: In comparison with LOCD patients, SERT availability was significantly higher in the putamen of EOCD patients (U = 4, p = .026), but not in the caudate nucleus (U = 14, p = .589), thalamus (U = 16, p = .818), and dorsal raphe nucleus (U = 7, p = .093). Binding potential of putamen showed a negative correlation (r = −.580, p = .048) with age of onset of the disease, but not with the Yale–Brown Obsessive Compulsive Scale scores.

Conclusions: These findings indicate that the earlier the age of onset of OCD, the less serotonergic pathology there is and that this difference remains even after long-term serotonin reuptake inhibitor treatment. Clinically, it might suggest that nonserotonergic treatments would be a better option for EOCD patients.

KEYWORDS

[^{11}C]DASB PET, age of onset, escitalopram, obsessive–compulsive disorder, serotonin transporter

1 | INTRODUCTION

Obsessive–compulsive disorder (OCD) is a common and disabling mental health condition, which is characterised by intrusive thoughts and related compulsive behaviours that are associated with significant levels of distress and interference (American Psychiatric Association, 2013). The neurotransmitter serotonin plays a pivotal role in the pathology of this disorder, as supported by findings that a range of serotonin reuptake inhibitors (SRIs), from earlier SRIs such as tricyclic antidepressants (Fernandez Cordoba & Lopez-Ibor Alino, 1967) to later ones such as selective SRIs (SSRIs), have therapeutic efficacy in OCD.

Recent evidence suggests that early-onset (EOCD) and late-onset forms of OCD (LOCD) may be distinctive subgroups stemming from different neurological bases. Studies comparing them have found notable contrasts in a range of aspects, including familial aggregation (Nestadt et al., 2000), comorbidity with tic disorder (Lochner & Stein, 2003; Millet et al., 2004; Rosario-Campos et al., 2001), symptom domains (Lochner & Stein, 2003; Millet et al., 2004; Tukel et al., 2005; Uguz, Askin, Cilli, & Besiroglu, 2006), symptom severity (Lomax, Oldfield, & Salkovskis, 2009; Rosario-Campos et al., 2001), and neuropsychological profiles (Hwang et al., 2007). Several studies have also found that EOCD patients are less likely to respond to SRI pharmacotherapies (Ackerman, Greenland, Bystritsky, Morgenstern, & Katz, 1994; Lochner & Stein, 2003; Rosario-Campos et al., 2001) and that they took a longer time and had to have a greater number of drug trials to achieve the remission (Fontenelle, Mendlowicz, Marques, & Versiani, 2003), although some reports found no difference in treatment response between groups (Uguz et al., 2006).

Previous molecular imaging studies on the serotonin transporter (SERT) have shown that OCD patients have lower SERT availability than controls (Matsumoto et al., 2010; Reimold et al., 2007). However, Hesse et al. (2011) reported that this is not the case for drug-naïve EOCD subgroup, showing that SERT availability is higher in drug-naïve EOCD than in LOCD. However, with SSRI treatment, SERT undergoes remodelling and relocalisation (Descarries & Riad, 2012), and it is still unknown whether the difference in SERT availability between subgroups persists following pharmacotherapy with SSRI.

The main aim of this paper is to examine the difference in SERT availability between medicated EOCD and LOCD, by analysing the availability of SERT using in vivo neuroimaging. In this study, we used [^{11}C]DASB, a SERT-specific radioligand (Houle, Ginovart, Hussey, Meyer, & Wilson, 2000), and escitalopram, one of the most serotonin-selective SSRI (Owens, Knight, & Nemeroff, 2001).

2 | METHODS

The protocol of this study was approved by the Institutional Review Board of Seoul National University Hospital, Seoul, Korea. All procedures in this study followed the recommendations of the Helsinki Declaration of 1975, as revised in 2008. The patients participated in the case–control study as described in Kim et al. (2016), and this is a subgroup analysis report according to the age of onset.

Twelve male patients meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnostic criteria for OCD were enrolled from the outpatient clinic in Seoul National University Hospital. Six patients who had onset of OCD before age 17 were identified as EOCD patients, whereas the other six patients who had their disease after age 17 or later were regarded as LOCD patients. This threshold was consistent with most of the previous studies (Fontenelle et al., 2003; Hesse et al., 2011; Tukel et al., 2005; Uguz et al., 2006).

Patients with a history or clinical evidence of significant medical conditions, or any comorbid psychiatric conditions requiring concomitant psychopharmacotherapy other than escitalopram were excluded.

Patients underwent serial [^{11}C]DASB positron emission tomography (PET) scans, which were taken 3, 24, and 72 hr after the last administration of escitalopram. For the measurement of plasma escitalopram concentration, blood samples were drawn 5 min before each PET scan. The symptom severity was assessed using the Yale–Brown Obsessive Compulsive Scale (YBOCS; Goodman et al., 1989).

Because the patients were on maintenance therapy with escitalopram, drug-free SERT binding potential (BP) was calculated using two-compartmental pharmacokinetic modelling based on the measured plasma concentration of escitalopram, followed by an inhibitory I_{max} pharmacodynamic modelling of which Kim et al. (2016) previously confirmed the validity in estimating the "baseline" drug-free BP. The primary regions of interest selected were putamen, caudate nucleus, thalamus, which consist of the cortico–striato–thalamo–cortical loop (Pauls, Abramovitch, Rauch, & Geller, 2014), and dorsal raphe nucleus (DRN), where serotonergic neurons are located. For the details on the pharmacokinetic–pharmacodynamic modelling processes, see the Supporting Information.

Statistical differences in drug-free SERT BP between EOCD and LOCD patients were examined by a Mann–Whitney *U* test. Pearson correlation analysis was used for the correlation between drug-free BP and age of onset, duration of illness, exposure to SSRIs, and YBOCS scores.

3 | RESULTS

The average (±standard deviation (SD)) age of illness onset was 13.0 ± 1.7 years for EOCD patients and 21.2 ± 2.7 years for LOCD patients, and it differed significantly between these subgroups of patients ($U = 36$, $p = .002$). Duration of illness (±*SD*), which equals to the age minus the age of onset, was 12.0 ± 6.4 for EOCD and 4.0 ± 2.5 years for LOCD patients and differed significantly between the groups ($U = 2.5$, $p = .009$). The escitalopram dose was 35.0 ± 20.7 mg for EOCD and 46.7 ± 18.6 mg for LOCD patients, which did not differ between groups ($U = 24.5$, $p = .310$). The mean age, duration of SSRI treatment, and the symptom severity also did not differ significantly between EOCD and LOCD patients (Table 1).

Mean drug-free SERT BPs (±*SD*) of putamen, caudate nucleus, thalamus, and DRN estimated with the I_{max} modelling were

TABLE 1 Demographic data (±*SD*)

	EOCD (*n* = 6)	LOCD (*n* = 6)	*p* value[a]
Age (years)	25.0 ± 6.4	25.2 ± 4.4	.589
Age of onset (years)	13.0 ± 1.7	21.2 ± 2.7	.002
Duration of illness (years)	12.0 ± 6.4	4.0 ± 2.5	.009
Exposure to SSRI (weeks)	91.8 ± 109.6	55.7 ± 61.1	.818
Escitalopram dose (mg)	35.0 ± 20.7	46.7 ± 18.6	.310
YBOCS scores			
(Total)	19.3 ± 5.6	17.0 ± 2.8	.485
(Obsession)	10.2 ± 2.5	10.0 ± 3.7	.699
(Compulsion)	9.2 ± 3.4	7.0 ± 3.7	.394

Note. EOCD = early-onset obsessive–compulsive disorder; LOCD = late-onset obsessive–compulsive disorder; SSRI = selective serotonin reuptake inhibitor; YBOCS = Yale–Brown Obsessive Compulsive Scale.

[a]Mann–Whitney *U* test.

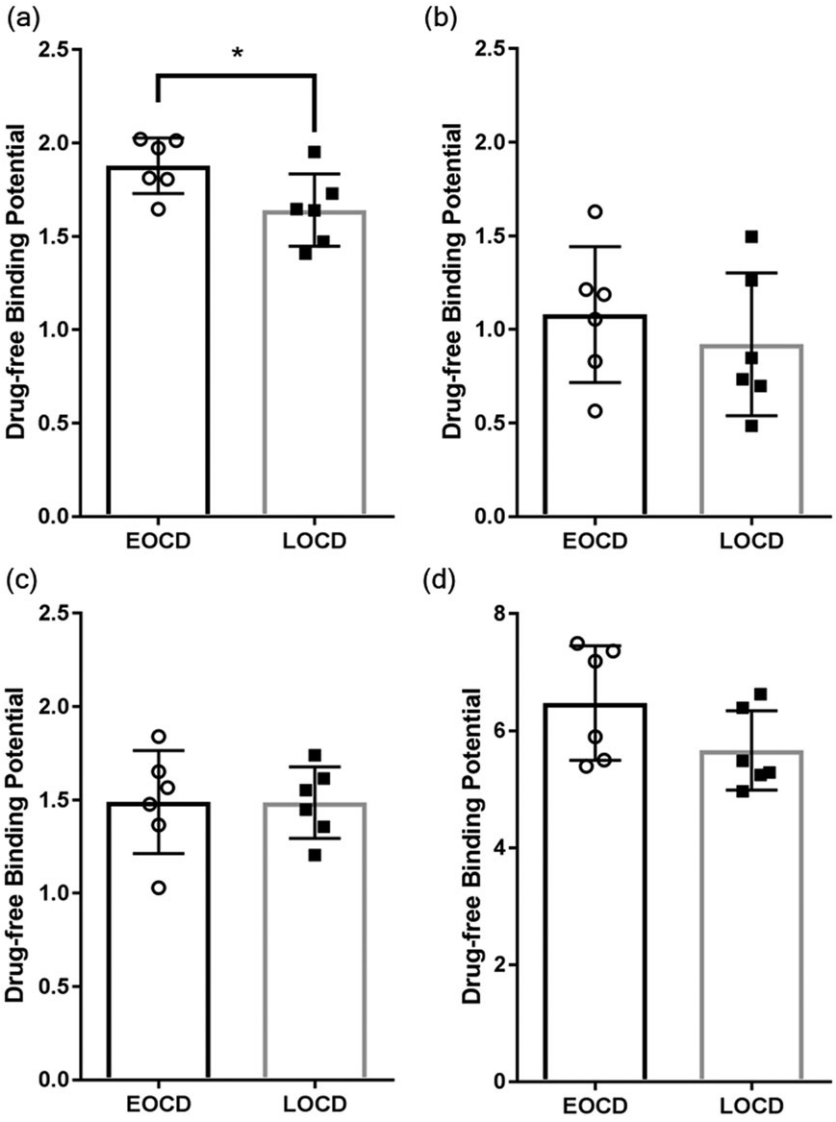

FIGURE 1 Drug-free serotonin transporter binding potentials in brain regions of early-onset and late-onset obsessive–compulsive disorder patients under the maintenance therapy with escitalopram. (a) Putamen, (b) caudate nucleus, (c) thalamus, and (d) dorsal raphe nucleus. EOCD = early-onset obsessive–compulsive disorder; LOCD = late-onset obsessive–compulsive disorder. *Statistically significant difference with the Mann–Whitney *U* test ($p < .05$)

1.88 ± 0.14, 1.08 ± 0.36, 1.49 ± 0.28, and 6.47 ± 0.98 for EOCD patients and 1.64 ± 0.19, 0.92 ± 0.38, 1.49 ± 0.19, and 5.67 ± 0.68 for LOCD patients. Drug-free SERT BP of the putamen differed significantly between EOCD and LOCD ($U = 4$, $p = .026$). Those of caudate ($U = 14$, $p = .589$), thalamus ($U = 16$, $p = .818$), and DRN ($U = 7$, $p = .093$) were not different between the groups, yet trends towards lower drug-free SERT BPs for LOCD patients were observed (Figure 1).

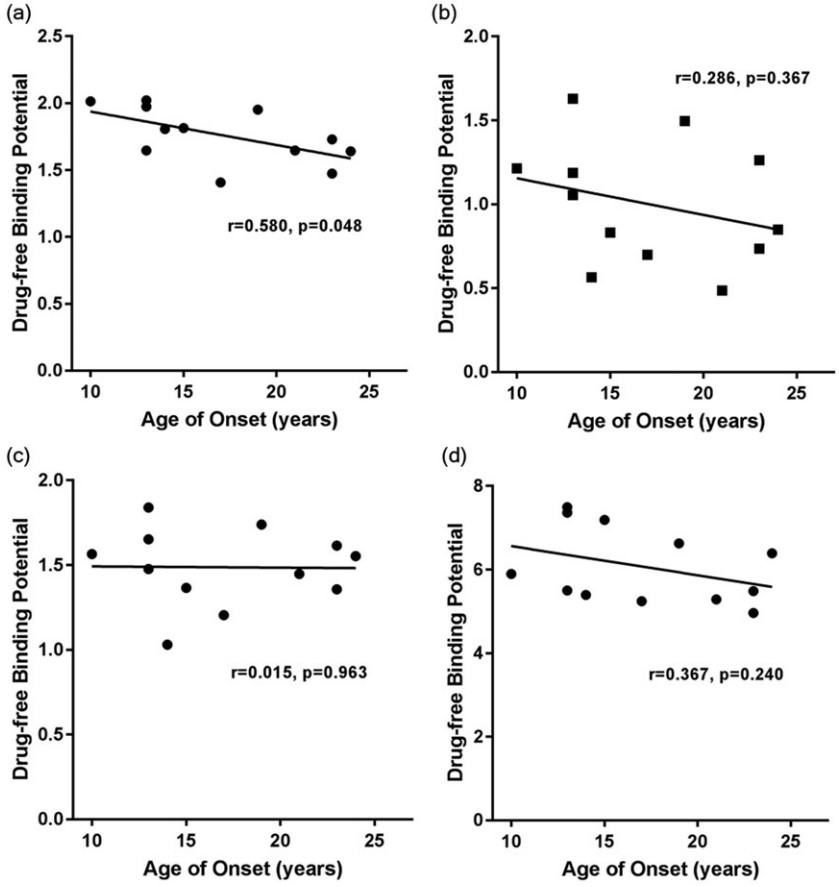

FIGURE 2 Correlation between the age of onset and the drug-free serotonin transporter binding potential in obsessive–compulsive disorder patients under the maintenance therapy with escitalopram. (a) Putamen, (b) caudate nucleus, (c) thalamus, and (d) dorsal raphe nucleus

A significant correlation was observed between the drug-free SERT BP in the putamen and the age of onset (r = −.580, p = .048, Figure 2), but not in the caudate nucleus, thalamus, or DRN.

The sensitivity analysis revealed no significant correlation between drug-free SERT BP and duration of illness (r = .422, p = .172), duration of exposure to SSRI (r = .400, p = .198), escitalopram dose (r = −.346, p = .271), or YBOCS total score (r = .096, p = .766), in the putamen.

4 | DISCUSSION

It has been consistently reported by PET studies using [^{11}C]DASB that OCD patients have lower SERT availability than controls (Matsumoto et al., 2010; Reimold et al., 2007). Thus, higher SERT availability in EOCD than LOCD in key brain regions in drug-naïve patients (Hesse et al., 2011) suggests that EOCD patients may have less degree of serotonergic pathology. However, we report that the higher SERT availability in EOCD remained even after long-term SSRI treatment, which indicates that long-term pharmacotherapy may not affect the difference in serotonergic pathology between subgroups. In addition, the negative correlation between the drug-free BP and age of onset implies that the earlier OCD was developed, the less degree of serotonergic pathology there is. It may explain why EOCD patients have poorer treatment response on SRIs (Ackerman et al., 1994; Lochner & Stein, 2003; Rosario-Campos et al., 2001) and the more number of trials of pharmacotherapy (Fontenelle et al., 2003). Thus, it can be also suggested that nonserotonergic treatments might be a better option than pharmacotherapy in treating EOCD patients, which is consistent with prior studies showing that OCD patients with comorbid tic disorder, whose onset is likely to be adolescence, respond better to dopaminergic pharmacotherapy such as antipsychotics (Bloch et al., 2006; McDougle et al., 1994), further supporting the idea that EOCD patients may have different pathophysiology from LOCD, for example, the dopaminergic one.

We have found no correlation between the drug-free BP and YBOCS scores in either groups, whereas the majority of previous studies did not find any correlation (Matsumoto et al., 2010; Pogarell et al., 2003; Stengler-Wenzke, Muller, Angermeyer, Sabri, & Hesse, 2004; van der Wee et al., 2004), and several others reported negative correlation between BP in key brain regions of OCD patients and their YBOCS scores (Hesse et al., 2005; Reimold et al., 2007; Zitterl et al., 2007). A possible explanation for these inconsistent findings might be the heterogeneity of the target population, such as drug-naïve or drug-free patients, and imaging ligands used, such as [^{123}I]beta-CIT in previous studies.

The main limitation of this study is the small size of the sample. We found statistically nonsignificant tendencies of higher drug-free BP in other key brain regions than the putamen, such as caudate nucleus and DRN in EOCD patients, and further studies with larger samples would help in clarifying such differences in those regions. In addition, pretreatment YBOCS score of the patients was not available, and hence, the difference of treatment response between groups could not be addressed in these data.

Notwithstanding the limitations, this study comes with several strengths. This is the first report studying medicated EOCD and LOCD

patients, which enhances our knowledge of the contrasting pathophysiology between the subgroups, including treatment response to SRIs. In addition, this study minimised bias using specific methods and population, such as the most selective SSRI, escitalopram as a drug (Owens et al., 2001), a highly SERT-selective ligand, [^{11}C]DASB (Houle et al., 2000), as a radioligand, and recruited OCD patients who were free of major comorbid disorders.

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CONFLICT OF INTEREST

Dr. Howes has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organised by Astra-Zeneca, Autifony, BMS, Eli Lilly, Heptares, Janssen, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand, and Roche. Neither Dr. Howes nor his family have been employed by or have holdings or a financial stake in any biomedical company.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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