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A longitudinal event-related potential study of selective serotonin reuptake inhibitor therapy in treatment-naïve pediatric obsessive compulsive disorder patients

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ABSTRACT

Obsessive-compulsive disorder (OCD) is characterized by obsessive thoughts and/or compulsive behaviors, involving specific cognition and/or information processing disorders. Event-related potentials (ERPs) are commonly used as physiological measures of cognitive function. In conscious patients, ERPs are easily and non-invasively measured. Previous ERP studies have revealed differences between OCD patients and control subjects. Whether ERPs reflect the pharmacological effects of OCD treatment, particularly in treatment-naïve pediatric patients, remains unknown. We used the Child's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) to evaluate the symptomatic severity of 12 treatment-naïve pediatric OCD patients. Comparisons were made with 12 age-, sex-, and intelligence-matched controls. The P300 and mismatch negativity (MMN) components were measured during an auditory odd-ball task at baseline in both groups and after the 3-year serotonin reuptake inhibitor (SSRI) treatment in OCD patients. Compared with controls, P300 amplitudes were smaller n the OCD group at Fz, Cz, Pz, C3, and C4. After SSRI treatment, P300 amplitudes increased partly at Fz and C4 in association with symptomatic improvements. We found a significant positive correlation between P300 amplitude in C4 and CY-BOCS scores. Our findings confirm the utility of SSRIs in pediatric OCD, and suggest the utility of ERPs for evaluating pharmacological effects in treatment-naïve pediatric OCD patients.

1. Introduction

Obsessive-compulsive disorder (OCD) is defined by the presence of intrusive thoughts (obsessions) and the need to perform repetitive behaviors (compulsions) that severely impair quality of life (Leckman et al., 2010). In particular, pediatric OCD is estimated to affect 1–3% of the pediatric population (Thomsen, 2013), and it is associated with significant functional impairment (Bipeta et al., 2013; Storch et al., 2010).

Recent advancements in the treatment of OCD have led to new insights into specific treatment-related outcomes. In particular, the efficacy of selective serotonin reuptake inhibitors (SSRIs) and behavioral therapy have been demonstrated by several placebo-controlled studies (Abramowitz, 1997; Sanchez-Meca et al., 2014; Van et al., 1994). Therefore, the first-line treatment for OCD includes SSRIs and behavioral therapy. In fact, SSRIs are the primary pharmacological treatment option for OCD (Dougherty et al., 2004). However, little is known about the long-term outcomes of pediatric patients with OCD (Berg et al., 1989; Cook et al., 2001; Stewart et al., 2004; Valleni-Basile et al., 1994). Few studies have reported long-term follow-up results in pediatric OCD patients. Furthermore, the existing literature is conflicting. In one study,

Abbreviations: OCD, obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitors; ERPs, event-related potentials; ADHD, attention deficit/hyperactivity disorder; MMN, mismatch negativity; SCID-NP, Structured Clinical Interview for DSM-IV Axis Disorders, Non-Patient Edition; K-SADS-PL, Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; WISC-IV, Wechsler Intelligence Scale for Children, 4th Edition; CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale; EEG, electroencephalography; PET, positron emission tomography; fMRI, functional magnetic resonance imaging; FIQ, full-scale intelligence quotient; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR); ICD-10, International Classification of Diseases, 10th edition

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early age OCD onset was associated with a longer disease duration (Stewart et al., 2004). In contrast, a study with longer follow-up periods found that a later age of onset was associated with OCD persistence (Bloch et al., 2009). Recently, three studies of pediatric OCD with longer follow-up periods reported that early treatment intervention prior to the onset of substantial functional impact predicted a better outcome (Bloch et al., 2009; Mancebo et al., 2014; Micali et al., 2010). Given the inconsistent observations of long-term course and outcome patterns in pediatric OCD, additional research is required.

Structural and functional neuroimaging studies of adolescents and adults with OCD suggest an impairment of the cortico-thalamic-striatal-cortical circuitry (Graybiel and Rauch, 2000; Menzies et al., 2008; Saxena et al., 2001a, 1998) that results in the disinhibition of abnormal or maladaptive habits, over which patients are unable to exert sufficient cognitive control (Graybiel and Rauch, 2000; Saxena et al., 2001b). Event-related potentials (ERPs) are commonly used as a physiological measure of cognitive function because they are easily and non-invasively recorded in conscious patients. Indeed, ERP measurements have permitted the exploration of underlying neurophysiological mechanisms and characteristics of cognitive dysfunction in several psychiatric disorders, including pediatric OCD (Yamamuro et al., 2015) and attention deficit/hyperactivity disorder (ADHD) (Janssen et al., 2016). The P300 component is an established index of information processing that is characterized as a peak observed approximately 300 ms after stimulus onset. P300 has been used to assess the mechanisms controlling the amount of information brought into consciousness (Picton, 1992), those updating the mental model of the environment to generate appropriate responses (Linden, 2005), and those involved in template matching (Hillyard et al., 1971). Moreover, P300 has been reported to occur across a widely distributed network, including the medial temporal lobe, temporoparietal junction, orbitofrontal cortex, and cingulate cortex (Brazdil et al., 2005; Linden, 2005; Mulert et al., 2004). Mismatch negativity (MMN) is another component that occurs during distinctive stimulus discrimination processing using sensory memory, which is considered to be important for the rapid detection of changes in the outside world (Jonkman et al., 1997). Accordingly, MMN reflects an automatic cerebral discrimination process that is not under conscious control. No study to date has investigated whether the P300 and MMN ERP components can be used to measure pharmacological and cognitive behavioral outcomes in pediatric OCD patients.

In the present study, we used ERPs to examine cognitive function during an auditory odd-ball task before and after SSRI treatment in treatment-naïve pediatric OCD patients. We hypothesized that pediatric patients with OCD would show abnormal P300 and MMN components, and that the affected ERPs would show at least partial improvement in parallel with clinical improvements after SSRI treatment. To test this, we measured ERPs during an auditory odd-ball task for pediatric patients with OCD and age- and sex-matched control subjects, and before and after SSRI treatment in pediatric patients with OCD.

2. Methods

2.1. Participants

We recruited 12 patients with OCD (5 males, mean age 13.60 ± 4.28 years and 7 females, mean age 13.43 ± 2.70 years) from the outpatient clinic at the Department of Psychiatry at Nara Medical University, Japan (Table 1). All patients were diagnosed with OCD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) and International Classification of Diseases, 10th edition (ICD-10). We also recruited 12 age- and sex-matched healthy control subjects. The absence of a psychiatric diagnosis was confirmed in the control group using a standard clinical assessment that included a psychiatric evaluation and a structured diagnostic interview (Structured Clinical Interview for DSM-IV Axis Disorders Non-Patient Edition; SCID-NP). All participants were right-handed and of Japanese descent. All participants and/or their caregivers provided written informed consent for their participation in the study. This study was approved by the Institutional Review Board at Nara Medical University.

Table 1
Participant characteristics.

	OCD group (n = 12)		Control group (n = 12)			
	Mean	SD	Mean	SD	*t*-value	*P*-value
Sex, boy/girl[a]	5/7		7/5			0.41
Age, years	13.50	3.26	13.83	2.41	0.78	0.78
FIQ (WISC-IV)	94.42	12.32	97.17	12.07	0.22	0.59
Onset, years	12.33	3.17	NA	NA	NA	NA
Duration, months	14.67	15.52	NA	NA	NA	NA
SSRI dose, mg	72.92	68.64	NA	NA	NA	NA

Abbreviations:FIQ, full-scale intelligence quotient; WISC-IV, Wechsler Intelligence Scale for Children, 4th Edition; SSRI, selective serotonin reuptake inhibitor; OCD, obsessive compulsive disorder; SD, standard deviation.

[a] A $\chi 2$ test was used for sex. Otherwise, a Student's *t*-test was used.

Patients were deemed eligible for inclusion if they had received a diagnosis of OCD according to the DSM-IV-TR, as described in the Kiddie Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) (Kaufman et al., 1997), and if their medical history had been evaluated by experienced psychiatrists. None of the OCD patients had comorbid ADHD, major depressive disorder, schizophrenia, autism spectrum disorder, epilepsy or tics, trichotillomania, or related repetitive behaviors. All selected patients were treatment-naïve and had not been medicated for OCD at the time of study onset. In this study, we defined the pre-SSRI condition as the period prior to the administration of SSRI pharmacotherapy, and the post-SSRI condition as the period approximately 3 years after the onset of SSRI pharmacotherapy.

Exclusion criteria included the presence of any neurological disorder, head injury, serious medical condition, or history of substance abuse/dependence. We assessed the intellectual level of all participants using the Wechsler Intelligence Scale for Children, 4th Edition (WISC-IV), and individuals with full-scale intelligence quotient (FIQ) scores below 70 were identified by a trained psychologist and excluded from the study. In total, 12 patients with OCD and 12 control subjects were enrolled.

2.2. Assessment of OCD symptoms

The Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) (Scahill et al., 1997) was used to evaluate symptoms in patients with OCD. The widely used CY-BOCS is a semi-structured, clinician-rated instrument that is designed to assess OCD severity and symptoms. Obsessions and compulsions are each rated on five items using a five-point scale (with scores ranging from 0–4) to assess multiple domains of OCD symptom severity, including time, interference, distress, resistance, and control. Consequently, the CY-BOCS yields an obsession score (0–20), a compulsion score (0–20), and a combined total score (0–40), with higher scores indicating greater symptom severity. The CY-BOCS has been demonstrated to have adequate convergent and divergent validity (Storch et al., 2006; Yucelen et al., 2006).