Reduced Prefrontal Activation in Pediatric Patients With Obsessive-Compulsive Disorder During Verbal Episodic Memory Encoding

Marcelo Camargo Batistuzzo, PsyD, PhD, Joana Bisol Balardin, PhD, Maria da Graça Morais Martin, MD, PhD, Marcelo Queiroz Hoexter, MD, PhD, Elisa Teixeira Bernardes, PsyD, Sonia Borcato, PsyD, Marina de Marco e Souza, PsyD, Cicero Nardini Querido, MD, Rosa Magaly Morais, MD, Pedro Gomes de Alvarenga, MD, Antonio Carlos Lopes, MD, Roseli Gedanke Shavitt, MD, PhD, Cary R. Savage, PhD, Edson Amaro, Jr., MD, PhD, Euripedes C. Miguel, MD, PhD, Guilherme V. Polanczyk, MD, PhD, Eliane C. Miotto, PsyD, PhD

Objective: Patients with obsessive-compulsive disorder (OCD) often present with deficits in episodic memory, and there is evidence that these difficulties may be secondary to executive dysfunction, that is, impaired selection and/or application of memory-encoding strategies (mediation hypothesis). Semantic clustering is an effective strategy to enhance encoding of verbal episodic memory (VEM) when word lists are semantically related. Self-initiated mobilization of this strategy has been associated with increased activity in the prefrontal cortex, particularly the orbitofrontal cortex, a key region in the pathophysiology of OCD. We therefore studied children and adolescents with OCD during uncued semantic clustering strategy application in a VEM functional magnetic resonance imaging (fMRI)–encoding paradigm.

Method: A total of 25 pediatric patients with OCD (aged 8.1-17.5 years) and 25 healthy controls (HC, aged 8.1-16.9) matched for age, gender, handedness, and IQ were evaluated using a block design VEM paradigm that manipulated semantically related and unrelated words.

Results: The semantic clustering strategy score (SCS) predicted VEM performance in HC ($p < .001$, $R^2 = 0.635$), but not in patients ($p = .099$). Children with OCD also presented hypoactivation in the dorsomedial prefrontal cortex (cluster-corrected $p < .001$). Within-group analysis revealed a negative correlation between Yale–Brown Obsessive Compulsive Scale scores and activation of orbitofrontal cortex in the group with OCD. Finally, a positive correlation between age and SCS was found in HC ($p = .001$, $r = 0.635$), but not in patients with OCD ($p = .936$, $r = 0.017$).

Conclusion: Children with OCD presented altered brain activation during the VEM paradigm and absence of expected correlation between SCS and age, and between SCS and total words recalled. These results suggest that different neural mechanisms underlie self-initiated semantic clustering in OCD.

Key Words: obsessive-compulsive disorder, functional magnetic resonance imaging, verbal episodic memory, semantic clustering

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Obsessive-compulsive disorder (OCD) is a debilitating condition with a lifetime prevalence varying between 1% and 3%.[1–3] Symptoms commonly begin in childhood and persist chronically in 30% to 40% of individuals, despite treatment.[4,5] The most widely accepted neurobiological hypotheses focus on a dysfunction of the cortico–striatal–thalamic–cortical (CSTC) loop, which integrates the prefrontal cortex (PFC) with different regions in the basal ganglia.[6-11] Consistent with this model, the literature has shown cognitive deficits related to PFC functioning in both adult[12] and pediatric[13-15] OCD samples. One of the most consistent neuropsychological findings is disruption in episodic memory,[16-21] which has been recently shown to be the most consistently impaired cognitive function in adults with OCD in 2 independent meta-analyses.[22,23] In general, neuropsychological studies with pediatric OCD samples have also found the same pattern of cognitive deficits,[13-15,20,24] including memory, that could be related to deficits in the CSTC circuitry.

Different hypotheses have been proposed to explain the observed episodic memory deficits in OCD. Since several studies have demonstrated that patients with OCD as well as controls retain long-term information, the possibility of memory storage and retrieval impairment has been excluded.[18,25,26] Hence, the focus of the neuropsychological studies has turned to the encoding/acquisition stage of memory. It has been hypothesized that patients with OCD might fail to "forget" irrelevant material learned during encoding, which would lead to impairment in the retrieval of relevant content.[27] However, Konishi *et al.* demonstrated that patients with OCD showed normal performance on a

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"directed forgetting" task.[27] An alternative explanation holds that memory deficits in OCD are mediated by poor executive functioning, such as strategic organization of stimuli to enhance memorability.[16,17,28-30] Thus, executive dysfunction could contribute to impairments at the encoding phase of episodic memory, which in turn could lead to deficits in delayed recall. Deficits in executive function are also consistently reported in neuropsychological studies of patients with OCD[25,26] and are directly linked to dorsolateral PFC (dlPFC), dorsomedial PFC (dmPFC), and orbitofrontal cortex (OFC) functioning, consistent with neuroimaging findings of OCD.[6-8] The hypothesis that executive function impairment mediates episodic memory deficits has accordingly received considerable attention.[16,17,28-32]

One example of executive dysfunction in episodic memory is failure to use strategies during encoding. A common strategy for learning word lists is semantic clustering, as grouping semantically related words into categories during encoding facilitates the delayed recall of verbal episodic memory (VEM).[33] Patients with OCD have difficulties in semantic clustering during encoding, and this has been related to their impaired delayed memory performance.[16,18,30,32] However, when trained to apply strategies during encoding, patients with OCD perform similarly to controls on delayed recall, which supports the mediation hypothesis.[31,32] Although the literature has replicated the mediation hypothesis in the adult population, little is known about this hypothesis in children and adolescents with OCD.

Imaging studies in healthy adults have shown that prefrontal regions such as the dlPFC[34,35] and the inferior frontal gyrus (IFG)[36,37] are involved in VEM encoding and semantic clustering.[38,39] Apart from these regions, a positron emission tomography (PET) study, also evaluating healthy adults, found positive correlations between brain activity in OFC and spontaneous initiation of semantic clustering strategies during VEM encoding.[36] Although the OFC is one of the most well-studied and replicated regions with a suggested key role in the neurobiological model of OCD,[9-11] there are no studies evaluating cerebral functioning of OCD pediatric patients during semantic clustering and VEM encoding. This is of interest because previous functional neuroimaging studies with this population have suggested abnormal PFC functioning (including dlPFC, dmPFC, IFG, and OFC) using other cognitive paradigms besides VEM.[40-43] This research would link the observed memory problems in children with OCD to brain networks implicated in the pathophysiology of the condition.

As children with OCD also demonstrate behavioral deficits in VEM tests,[13,17,21,32] we decided to investigate the neural correlates (especially the regions mentioned above) of VEM by manipulating strategy use during the encoding phase of VEM with a functional magnetic resonance imaging (fMRI) paradigm in a sample of pediatric patients with OCD. If the mediation hypothesis is true, these deficits could be explained as failures to self-initiate organizational strategies during memory encoding.[16] Thus, our primary objective was to investigate the neural correlates of semantic strategy application during verbal memory encoding in children and adolescents with OCD. We hypothesized that children with OCD would perform worse on the behavioral measures of the paradigm (i.e., would make fewer semantic associations and remember fewer words) and would present different patterns of activations (blood oxygen level–dependent [BOLD] effect alterations) in frontal regions (OFC, IFG, and dlPFC) when compared to typically developing controls.

TABLE 1 Demographic and Clinical Characteristics

	OCD (n = 25)	Controls (n = 25)	*p*
Gender, n (%)			
Male	14 (56)	14 (56)	1.000[c]
Pubertal development, mean (SD)			
Age, y	12.7 (2.6)	12.2 (2.4)	.433[a]
Petersen Puberty Scale	5.2 (4.3)	6.4 (3.9)	.348[a]
Handedness, n (%)			
Right	25 (100)	25 (100)	1.000[c]
Education level			
Education, y, mean (SD)	7.4 (2.5)	6.5 (2.5)	.177[a]
Grade retentions, n (%)	4 (16)	1 (4)	.189[c]
IQ, mean (SD)	102.1 (14.5)	99.6 (13.3)	.532[a]
Y-BOCS, mean (SD)			
Total	27.2 (5.0)	0 (0.0)	**<.001**[a]
Obsessions	12.9 (3.1)	0 (0.0)	**<.001**[a]
Compulsions	14.1 (3.1)	0 (0.0)	**<.001**[a]
Anxiety, mean (SD)			
SCARED	26.7 (14.8)	6.6 (9.9)	**<.001**[b]
Depression, mean (SD)			
CDRS-R	29.6 (16.8)	17.0 (0.2)	**<.001**[a]
Routines, mean (SD)			
CRI	43.4 (16.0)	21.8 (3.9)	**<.001**[a]

Note: Boldface denotes significant p values. CDRS-R = Children's Depression Rating Scale–Revised; CRI = Childhood Routines Inventory; OCD = obsessive-compulsive disorder; SCARED = Screen for Child Anxiety Related Emotional Disorders; Y-BOCS = Yale–Brown Obsessive-Compulsive Scale.

[a] *Student t test for independent samples.*

[b] *Mann–Whitney test.*

[c] *χ^2 Test.*

METHOD

Design and Participants

This was a cross-sectional study including 25 children and adolescents with OCD (age range, 8.1–17.5 years) from the OCD Spectrum Disorders Program, Department of Psychiatry, University of São Paulo Medical School and the National Institute of Developmental Psychiatry for children and adolescents. All patients met *DSM-IV-TR* criteria for OCD and were recruited from February 2011 to December 2012.

The inclusion criteria involved the following: age less than 18 years; OCD as the main diagnosis, with a minimum Yale–Brown Obsessive Compulsive Scale (Y-BOCS)[44] score of 16, or 10 for only obsessions or compulsions; absence of OCD treatment (pharmacological or psychotherapy) for at least 15 days, and adequate reading fluency. Patients were excluded if they had any of the following: previous head injury, cysts, or any brain malformation; history of substance abuse; presence of psychotic symptoms, schizophrenia,