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Cognitive Planning Neural Correlates in a Pediatric Monozygotic Twin Pair Discordant for Obsessive-Compulsive Disorder: Exploring Potential Application in Precision Medicine

To the Editor: Pediatric obsessive-compulsive disorder (OCD) is a debilitating illness characterized by intrusive thoughts and repetitive behaviors. Patients may exhibit poorer executive function, such as cognitive planning.¹ Substantial overlap exists between brain areas implicated in OCD pathology² and those involved in planning (eg, dorsolateral prefrontal cortex, posterior parietal cortex, extrastriate visual cortex, anterior cingulate cortex, inferior frontal gyrus),³ and functional magnetic resonance imaging (MRI) demonstrates that participants with OCD perform poorly and show less regional brain responsivity as task load increases in comparison to healthy controls.⁴ This robust finding could be useful in the domain of precision medicine, as it normalizes after cognitive-behavioral therapy⁵ and may be useful in individual activation profiles that could predict treatment response. However, the finding has never been studied in individual subjects. Here, as a proof of concept, we compare the performance and brain activation of OCD-discordant monozygotic twins during a planning task commonly used in imaging studies,⁶ the Tower of London (ToL).

Methods. A pair of monozygotic Caucasian twins discordant for pediatric OCD and their parents consented to the study, in compliance with approval from the local institutional review board. All collected data were deidentified to protect anonymity. The Wechsler Abbreviated Scale of Intelligence Second Edition (WASI-II),⁷ the Cambridge Neuropsychological Test Automated Battery (CANTAB),⁸ and the Children’s Yale-Brown Obsessive Compulsive Scale (CY-BOCS)⁹ were administered.

Structural and functional MRI were recorded on a GE MR750 3T MR scanner when the twins were 12 years old. The OCD-affected twin was experiencing severe OCD symptoms (CY-BOCS score = 29/40) and had been taking clomipramine 50 mg and fluvoxamine 100 mg daily for 4 weeks prior to the scan. The unaffected twin reported no OCD symptoms and was taking no medication.

Results. During neurocognitive testing, the OCD-affected twin displayed general cognitive functioning in the superior range (Full Scale Intelligence Quotient, 93rd percentile) and verbal intelligence in the very superior range (98th percentile). Visuospatial information

processing and reasoning were average (WASI-II Matrix Reasoning subtest, 70th percentile), as was spatial planning performance (CANTAB Stockings of Cambridge subtest, 75th percentile).

The unaffected twin also displayed general cognitive functioning in the superior range (97th percentile) and verbal intelligence in the very superior range (98th percentile). Consistent with her general cognitive functioning, but in contrast to her monozygotic twin, visuospatial information processing and reasoning were in the superior range (92nd percentile), and spatial planning performance was in the superior range (95th percentile).

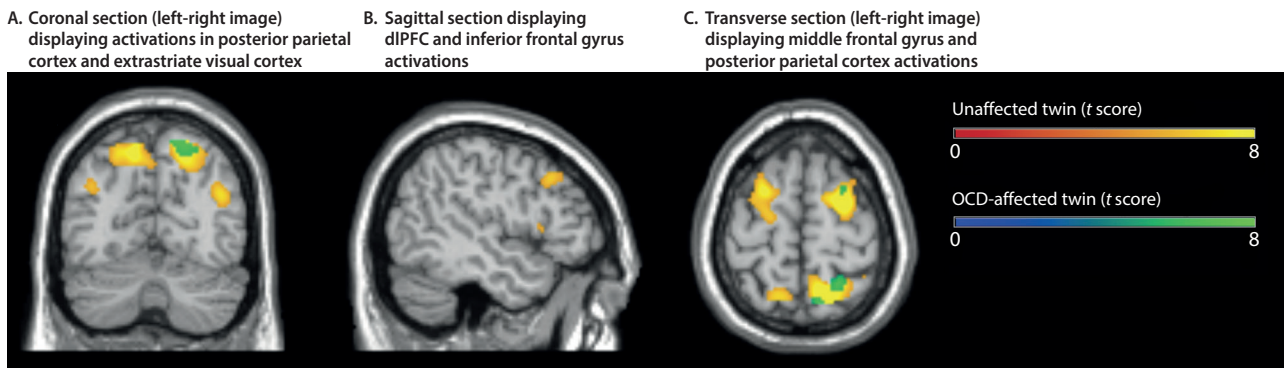
In the scanner, both twins performed well during low load ToL trials (98% accuracy), but the OCD-affected twin performed significantly worse (79% accuracy; 95% confidence interval, 69%–90%) than her unaffected twin (92% accuracy; 95% confidence interval, 85%–100%) during high load trials. As task load increased, the unaffected twin demonstrated activation of bilateral dorsolateral prefrontal cortex (dlPFC), as well as auxiliary areas such as the inferior frontal gyrus (IFG). The OCD-affected twin did not demonstrate increased dlPFC or IFG or compensatory brain activity as task load increased (Figure 1).

Studies have shown poorer cognitive planning in OCD patient groups.^{1,4} Group functional MRI studies of the ToL have linked these impairments to underrecruitment of the dlPFC and compensatory areas that should be involved as task load increases.⁴ The performance and brain activity of these twins demonstrate results consistent with the literature while using single-subject comparisons, providing proof of concept that the ToL may have a role in future precision medicine efforts. While the use of monozygotic twins ensured optimal matching on many key factors, a limitation of this study is that not all observed findings can be attributed solely to OCD discordance. Future work is necessary to develop tools and refine traditional neural probes for use in precision medicine.¹⁰

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Figure 1. Blood Oxygen Level–Dependent (BOLD) Signal Contrast for High Minus Low Task Load^a



^aStatistical threshold was set at $P < .01$, FWE-corrected for above figure. Note that when $P < .05$, FWE-corrected (not displayed), the OCD-affected twin also shows activations on the left posterior parietal cortex and middle front gyrus and but continues to show no dlPFC activation. Abbreviations: dlPFC = dorsolateral prefrontal cortex, FWE = familywise error rate, OCD = obsessive-compulsive disorder.

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