Assessing neurocognitive function in psychiatric disorders: A roadmap for enhancing consensus

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abstract

It has been challenging to identify core neurocognitive deficits that are consistent across multiple studies in patients with Obsessive Compulsive Disorder (OCD). In turn, this leads to difficulty in translating findings from human studies into animal models to dissect pathophysiology. In this article, we use primary data from a working memory task in OCD patients to illustrate this issue.

Working memory deficiencies have been proposed as an explanatory model for the evolution of checking compulsions in a subset of OCD patients. However, findings have been mixed due to variability in task design, examination of spatial vs. verbal working memory, and heterogeneity in patient populations. Two major questions therefore remain: first, do OCD patients have disturbances in working memory? Second, if there are working memory deficits in OCD, do they cause checking compulsions?

In order to investigate these questions, we tested 19 unmedicated OCD patients and 23 matched healthy controls using a verbal working memory task that has increased difficulty/task-load compared to classic digit-span tasks. OCD patients did not significantly differ in their performance on this task compared to healthy controls, regardless of the outcome measure used (i.e. reaction time or accuracy). Exploratory analyses suggest that a subset of patients with predominant doubt/checking symptoms may have decreased memory confidence despite normal performance on trials with the highest working memory load.

These results suggest that other etiologic factors for checking compulsions should be considered. In addition, they serve as a touchstone for discussion, and therefore help us to generate a roadmap for increasing consensus in the assessment of neurocognitive function in psychiatric disorders.

1. Introduction

An increasing number of psychiatric researchers are attempting to translate findings from humans into animals, in an effort to leverage animal models to dissect the molecular and cellular abnormalities that underlie deficits in core cognitive processes central to neuropsychiatric disorders. This strategy takes advantage of the strength of animal systems, including the recent development of technologies that allow precise activation and inhibition of specific neural circuits on a variety of timescales (i.e. optogenetics and chemogenetics) (Dong, Rogan, & Roth, 2010; Gradinaru et al., 2010; Mattis et al., 2012; Rogan & Roth, 2011; Schneider, Gradinaru, Zhang, & Deisseroth, 2008; Sparta et al., 2012; Zhang et al., 2010), as well as the ability to regulate expression of genes of interest with spatial and temporal specificity (Donaldson & Hen, 2014; Donaldson, Nautiyal, Ahmari, & Hen, 2013). With these tools we can now determine how abnormalities in specific neural circuits lead to changes in cognitive function. This information can be used to elucidate the potential neural mechanisms underlying similar cognitive abnormalities characteristic of neuropsychiatric disease in humans. However, to help bridge the gap between findings observed in animals and human neuropsychiatric illness, another important step is the identification of neurocognitive functions that are reliably abnormal in patient populations suffering from particular psychiatric illnesses. Despite significant efforts in this area, it remains challenging to identify consistently abnormal biomarkers within particular disease categories. Here, we will
discuss possible reasons for this difficulty from the viewpoint of Obsessive Compulsive Disorder (OCD), using working memory as an example of a neurocognitive domain.

OCD is a chronic, disabling neuropsychiatric disorder that affects between 1.5% and 3% of the world’s population according to epidemiological studies (Kessler et al., 2005; Rasmussen & Tsuang, 1984; Weissman et al., 1994). Despite its severity and high prevalence, there is still limited insight into the pathophysiology of OCD. This is due at least in part to the difficulty of identifying neurocognitive domains that are reliably abnormal in OCD patients, a key step in translating findings from patients into animal models (Abramovitch, Abramowitz, &ittelman, 2013; Shin, Lee, Kim, & Kwon, 2013). Though there are many points of controversy in the field, one question that leads to spirited debate is whether OCD patients have memory deficits when compared to healthy controls. In addition, memory deficiencies have been proposed as an explanatory model for how checking compulsions in a particular subtype of OCD might develop (Harkin & Kessler, 2011; Jaafari et al., 2013; Moritz, Jacobsen, Willenborg, Jelinek, & Fricke, 2006).

Checking compulsions are a prominent symptom in many OCD patients (Jaafari et al., 2013; Mataix-Cols et al., 2004; Rapoport, 1991; Swedo, Rapoport, Leonard, Lenane, & Cheslow, 1989). These abnormal repetitive behaviors are often linked to obsessive thoughts about potential catastrophic events, and are typically carried out in an attempt to prevent the harmful outcome from occurring. A classic example of a checking compulsion is repeatedly checking the door to make sure it has been locked properly; the corresponding obsession is the intrusive fear that the front door was not properly locked and harm will therefore come to one’s family. In the subgroup of OCD patients with predominant checking compulsions, it has been suggested that working memory deficits may play an etiological role in the generation of repetitive checking behavior (Jaafari et al., 2013; Moritz et al., 2006). In this explanatory model, OCD patients would literally not remember if they had checked the door lock properly, and would therefore need to repeat the behavior until they could retain the memory of locking the door. This model raises two key questions. First, do OCD patients in general have disturbances in working memory? And second, if there are working memory deficits in OCD, what is their relationship to OCD symptoms?

Although several studies over the past two decades have attempted to answer the first question, a review of the literature still yields inconsistent results (see Abramovitch et al. (2013) and Shin et al. (2013) for meta-analyses). For the purposes of this article, we will focus exclusively on behavioral data, and not address neuroimaging findings related to working memory tasks. Though spatial working memory deficits have been found in OCD patients compared to healthy controls, this has primarily occurred in situations where the load on the memory system is high. For example, low memory load levels in a spatial n-back task (0, 1, and 2) yield normal performance, but deficits have been found in a higher load 3 n-back task (Nakao et al., 2009; van der Wee et al., 2003, 2007). Similarly, Purcell et al. (1998a,b) found normal working memory during low-difficulty trials in a spatial search task, but demonstrated memory impairments in high-difficulty trials. Consistent with this pattern, using the CANTAB Spatial Working Memory task, Chamberlain et al. (2007) observed deficits for hard (up to 12 search locations), but not easy, difficulty levels. Notably, however, other results using the CANTAB task were mixed: Nedeljkovic et al. (2009) found normal working memory in OCD patients (Nedeljkovic et al., 2009), while Morein-Zamir et al. (2010) did not. Finally, in both the Backward Location Span Task (Jaafari et al., 2013), and the Operation-Span Task, a more complicated spatial working memory task that requires participants to retain a series of words while performing math problems (Grisham & Williams, 2013), OCD patients were impaired compared to healthy controls. However, despite these relatively cohesive results, other studies using either a delayed match-to-sample task (Ciesielski et al., 2007) or a spatial search task (Morein-Zamir et al., 2010) did not find working memory deficits.

While there has been less investigation of verbal working memory in OCD patients, the available data are likewise mixed. Martin, Wiggs, Altemus, Rubenste, and Murphy (1995), Cohen and et al. (1996), and Morein-Zamir et al. (2010) demonstrated normal working memory span in OCD patients using the WAIS-R Digit Span backward. However, there is some evidence for performance differences between OCD patients and healthy controls. For example, though Koch and et al. (2012) observed no differences in number of correct responses on a verbal n-back task, they did find that OCD patients performed the task more slowly than healthy controls did; it was suggested that this was evidence of a speed-accuracy trade-off. Similarly, Martin et al. (1995) also demonstrated decreased speed during task performance. Based on these results, together with the hypothesis that OCD patients would have verbal working memory deficits in tasks with a higher memory load, we tested whether OCD patients would demonstrate verbal working memory deficits in a more challenging test recently developed by Nee and Jonides called the Ignore-Suppress Task (Nee & Jonides, 2008a,b).

2. Methods

2.1. Participants

Nineteen OCD subjects and 23 healthy controls (HC) met eligibility requirements after screening. Groups were matched on age, gender, ethno-racial groups, and verbal IQ (measured using the National Adult Reading Test (NART)) Nelson and O’Connell (1978), (Table 1). All participants provided written informed consent after explanation of study procedures. The study protocol was approved by the Internal Review Board of New York State Psychiatric Institute/Columbia University.

2.2. Screening procedures and clinical assessment

Eligible participants were between ages 18 and 55, had no significant medical problems, were not pregnant or nursing, had no current or past neurological disorder (other than one participant with Tic Disorder – see Table 1), and were free of psychoactive medications. Because of known effects of hormonal state on working memory (Hampson & Morley, 2013), we excluded women who were using hormonal contraceptives or were pregnant or postmenopausal; we also consistently administered the task in the early follicular phase of the menstrual cycle (Day 1–10). OCD subjects met criteria from the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) for OCD for at least one year and had clinically significant symptoms (Yale-Brown Obsessive Compulsive Scale [Y-BOCS] score ≥ 16) (Goodman & et al., 1989). They had no other current Axis I disorder with five exceptions (one participant with Chronic Tic Disorder, one with Panic Disorder, one with Generalized Anxiety Disorder, one with Dysthymic Disorder, and one with Social Phobia and Binge-Eating Disorder; in all cases OCD was the principal diagnosis; and no lifetime diagnosis of psychotic disorder, bipolar disorder, mental retardation, or substance abuse/dependence. No OCD subjects were receiving OCD treatment at the time of study participation (either medication or cognitive-behavioral therapy [CBT]), and were free of all psychotropic medications for at least 4 months. HCs had no current or past DSM-IV Axis I or Axis II disorder, and had never taken psychotropic medication; in addition, none had a family history of psychotic disorders or ADHD (both of which have been associated with working
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