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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.

Keywords

Obsessive Compulsive Disorder (OCD); Ignore-Suppress; Working memory; Serotonin reuptake inhibitors (SRIs); Checking; Neurocognitive

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, & Mittelman, 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 and 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) observed deficits (Nedeljkovic & et al., 2009), while Morein-Zamir and 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 test 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, Rubenstein, 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 signed 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 memory abnormalities) (Alderson, Kasper, Hudec, & Patros, 2013; Barch & Smith, 2008) as assessed by the Family History Screen (Weissman & et al., 2000).

Psychiatric diagnoses were made by clinical interview and confirmed with Structured Clinical Interview for DSM-IV (Ekselius, Lindstrom, von Knorring, Bodlund, & Kullgren, 1994; First, Spitzer, Gibbon, & Williams, 2002). OCD and depressive severity were

assessed by a trained rater using the Y-BOCS (scale range: 0 to 40; 16 and above is considered clinically significant OCD) (Goodman et al., 1989, 1989), and the Hamilton Depression Rating Scale (HAM-D, 17-item, scale range: 0–50) (Hamilton, 1960). The Y-BOCS checklist was used to generate scores for each OCD participant along five different symptom dimensions (contamination and cleaning; taboo thoughts; doubt and checking; symmetry and ordering; and hoarding [though note, primary hoarding is now generally considered to be distinct from OCD, though it is part of the dimensional measures that have been developed using the Y-BOCS and therefore is included in this analysis]), using the procedure recommended by Pinto et al. (2007, 2008, 2009). The Yale Global Tic Severity Scale (YGTSS) was used to assess tics (Leckman & et al., 1989). Medical health was confirmed by physical exam, electrocardiogram, blood tests, and urinalysis. Urine pregnancy test and urine drug screen (Medical Disposables) were used to confirm that subjects were not pregnant or taking illicit substances, opiates, or benzodiazepines on the day of testing.

2.3. Task design

In both the Ignore and Suppress conditions of this task developed by Nee and Jonides (2008a,b), participants were presented with a word set (Fig. 1). Either before the word set was presented (in Ignore) or after the word set was presented (in Suppress), the participant was cued to retain a subset of the words. At the end of each trial, participants were probed with a word, and had to decide whether that word was one of the words in the to-be-remembered subset or not. The two conditions dissociate different types of inhibitory abilities: The Ignore condition taps inhibition at the level of perception, while the Suppress condition reflects inhibition in working memory.

2.4. Task procedure

Participants were tested on both the Ignore and Suppress tasks. In Ignore (Fig. 1A), the participant first saw an instruction to Attend to either the red or blue words, then 1 s later saw the 6-word memory-set for 4.5 s, then 3 s later saw a probe word. The participant was instructed to respond “Yes” if the probe matched one of the words that was supposed to be in working memory (POOL, TILL and PASS in Fig. 1A), and “No” otherwise. Responses were made by pressing either the 0 key (labeled “NO”) to indicate a negative response, or the 1 Key (labeled “YES”), to indicate a positive response. On 40% of the trials the probe matched one of the words that should have still been in working memory (TILL in Fig. 1A; Valid probes); on 30% of the trials the probe matched one of the words that should have been ignored and therefore required a negative response (RING in Fig. 1A; Lure probes); and on the remaining 30% of the trials the probe did not match any word presented in that trial (HEAT in Fig. 1A; Control probes).

In Suppress (Fig. 1B) the participant first saw the 6-word memory-set for 4.5 s, and then 1 s later saw an instruction to Remember only the words of one color (red or blue). The rest of the trial events—including the three types of probes—were the same as in the Ignore task. The major difference between Ignore and Suppress was when the critical instruction cue was given relative to the memory set. When the instruction occurred before the memory set—as in the Ignore task—selection could occur on perceptual representations prior to entry into

working memory, whereas when the instruction cue was given after the memory set—as in the Suppress task—selection could occur only in working memory. Overall, Lure Suppress trials had the highest working memory load.

Trials were blocked by task, with 10 trials per block. There were 5 blocks each of Ignore and Suppress trials, yielding 100 total observations per participant. Participants completed at least two practice blocks, one each of Ignore and Suppress, before beginning the experiment. Ignore and Suppress task blocks alternated, with the order of the blocks counterbalanced across participants. Feedback was given on practice trials but not experimental trials. Experimental tasks were delivered by computer and presented using E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA). The stimuli consisted of 80 four-letter nouns that have been used in previous studies with this paradigm (Nee & Jonides, 2008b, 2009; Smith, Eich, Cebenoyan, & Malapani, 2011).

2.5. Outcome measures

The outcome measures of major interest included mean Reaction Times (RT) calculated from correct trials only, and Accuracy [the proportion of overall correct responses- i.e. either saying ‘Yes’ on valid trials or ‘No’ on lure or control trials]. We also computed a contrast between performance on two kinds of negative probes: Lures, to which the participant should respond “No” because although the word was in the original memory-set, it should have been intentionally inhibited, and Controls, to which the participant should respond “No” because the word was not in the memory-set at all. If selection was perfect, there should be no difference between performance on Lure and Control probes; to the extent selection was poor, the difference between the two kinds of negatives would be large. More specifically, to the extent that selection was poor, a Lure probe would appear familiar, and participants would have to inhibit the tendency to respond positively on the basis of familiarity, which in turn would lengthen reaction times (Clarke, Robbins, & Roberts, 2008; Monsell, 1978; Smith & Jonides, 1998). Nee & Jonides (2008b) found that selection failure was greater in Suppress than Ignore in healthy younger adults, and that this difference could not be attributed to the overall difficulty of the tasks. In people with schizophrenia, we previously found that the difference-score was not significantly different for HCs and people with schizophrenia in the Ignore task (32.50 vs. 21.44 ms, respectively); however it was significantly different in the Suppress task (278.36 vs. 178.51 ms, respectively), suggesting breakdowns in cognitive control for information already in working memory in people with schizophrenia (Eich, Nee, Insel, Malapani, & Smith, 2014; Smith et al., 2011).

In addition, we calculated performance measures based on Signal Detection Theory (Green & Swets, 1966; Swets, Green, Getty, & Swets, 1978), as our task involved both ‘signal’ trials (Valid) and ‘noise’ trials (Lure and Control trials). These performance measures included; (1) Hit Rate (the proportion of Valid trials to which the subject responded ‘Yes’ correctly); (2) False Alarm Rate (the proportion of Lure and Control trials on which the participant responded ‘Yes’ incorrectly); (3) Criterion C, an index of bias in responding either ‘Yes’ or ‘No’ on the task as a whole, where a value of 0 indicates the absence of bias, a negative value indicates that the participant responds ‘Yes’ more often than the ideal observer, and a positive value indicates that the participant responds ‘No’ more often than

the ideal observer; and (4) Discriminability (or Sensitivity) Index (d'), which is an overall assessment of the participant's ability to distinguish signal from noise, calculated by combining information about the likelihood of correctly identifying a word given that the word was present in the to-be-remembered subset (e.g., correctly saying 'Yes' on Valid trials), with information about the likelihood of incorrectly identifying a word that was *not* in the to-be-remembered subset (e.g., saying 'Yes' on either Lure trials (the word should not have been retained) or Control trials (the word was not present at all)).

2.6. Statistical analysis

Groups were compared on demographics and clinical characteristics using independent t -tests for continuous variables and Chisquared for categorical variables. Group differences in accuracy and reaction time were assessed with repeated measures ANOVA, with 1 between-participant factor (Group: OCD vs. HC), and 2 within-participant factors (*Condition*: Ignore vs. Suppress; *Trial-Type*: Valid vs. Control vs. Lure). Because accuracy data were not normally distributed, a multilevel binomial regression was performed. Group differences in Signal Detection Theory Measures were assessed with independent t -tests. Spearman rank correlation was used for exploratory analyses to examine associations between Suppress findings and clinical features of the 19 OCD patients.

3. Results

3.1. Description of the sample

Demographic and clinical characteristics of the 19 OCD subjects and 23 HCs are shown in Table 1. OCD subjects did not significantly differ from HCs in gender (Chi-squared $p > .37$), ethnicity, age, or verbal IQ (estimated using the NART) (all p 's $> .57$). OCD subjects had clinically significant OCD symptoms, with mean YBOCS of 28 and range from 22 (i.e., moderate OCD) to 37 (i.e., extreme OCD). All five OCD symptom dimensions were represented (i.e., contamination and cleaning, taboo thoughts, doubt and checking, symmetry and ordering, and hoarding), and most patients had symptoms in more than one domain. Only three OCD subjects had symptoms restricted primarily to one domain (contamination and cleaning symptoms, $n = 1$; taboo thoughts, $n = 1$; symmetry and ordering, $n = 1$). One OCD subject met DSM-IV criteria for Chronic Tic Disorder. None of the OCD subjects reported pathologic grooming behaviors (e.g. trichotillomania, skin-picking). HCs had no evidence of OCD symptoms or depression on YBOCS or HAM-D, respectively.

All OCD subjects were free of psychotropic medication for at least four months prior to testing. The majority of OCD subjects (11/19; 52.6%) had never been exposed to serotonin reuptake inhibitors. Only one OCD patient (out of 19) had ever received CBT consisting of exposure and response prevention.

3.2. Ignore-Suppress

3.2.1. Reaction time—We performed a repeated-measures Analysis of Variance (rmANOVA) with 1 between-participant factor (Group: OCD vs. HC), and 2 within-participant factors (*Condition*: Ignore vs. Suppress; *Trial-Type*: Valid vs. Control vs. Lure). There was

a main effect of Condition such that RTs were slower for Suppress than Ignore [936.03 vs. 745.45 ms; $F(1, 40) = 67.17, p < .001, \eta_p^2 = .63$], and a main effect of Trial-Type such that Lure trials were the slowest and Control trials the fastest [917.61 = Lure, 806.74 = Valid, 797.77 ms = Control; $F(2, 80) = 49.61, p < .001, \eta_p^2 = .55$] (Fig. 2). There was also a significant two-way interaction between Condition and Trial-Type [$F(2, 80) = 27.88, p < .001, \eta_p^2 = .41$]. The main effect of Group was not significant, nor were any of the interactions where Group was a factor (Condition $\times$ Group, Trial-Type $\times$ Group (all F s < 1), and Condition $\times$ Trial-Type $\times$ Group ($F = 1.1$)).

3.2.2. Accuracy—An rmANOVA for accuracy revealed a main effect of Condition such that accuracy was higher in Ignore than Suppress (96.02% vs. 89.32%; $F(1, 40) = 28.81, p < .001, \eta_p^2 = .42$] (Fig. 3). The main effects of Trial-Type and Group were not significant ($F(2, 80) = 2.35$ and $F(1, 40) < 1$, respectively), nor were any of the interactions: Condition $\times$ Group; Trial-Type $\times$ Group; Condition $\times$ Trial-Type $\times$ Group (all F s < 1); Condition $\times$ Trial-Type $F(2, 80) = 2.48$. As the accuracy data were not normally distributed, we performed a multilevel binomial regression. This analysis revealed a main effect of Condition ($F(1, 4388) = 57.65, p < .001$), a main effect of Trial-Type ($F(2, 4388) = 6.02, p = .002$) and a significant interaction between Condition $\times$ Trial-Type ($F(2, 4388) = 6.69, p = .001$). Neither the main effect of Group, nor any of the interactions containing Group were significant (all F s < 1.2).

3.2.3. Difference scores—Difference scores were calculated to compare reaction times for Lure vs. Control negative probes. An ANOVA on the RT difference-scores between the two types of negatives (Lure-Control) with 1 between-participant factor (Group) and 1 within-participant factor (Condition) revealed a main effect for Condition—i.e. difference-scores were larger in Suppress than Ignore ($F(1, 40) = 45.97, p < .001, \eta_p^2 = .54$), as was expected—but not for either Group or for the two-way interaction between Condition and Group (F s < 1). An analogous ANOVA on Accuracy difference-scores between the two types of negatives (Lure-Control) revealed no significant effects for Condition, Group, or the two-way interaction between Condition and Group (all F s < 1).

3.2.4. Signal detection theory measures—Finally, we performed t -tests comparing HCs to OCD subjects on Hit Rate, False Alarm Rate, Criterion C, and d' . As illustrated in Table 2, there were no significant differences between HC and OCD subjects on any of these measures (all t s (1, 40) < 1).

3.3. Correlations between suppress measurements and clinical ratings

Exploratory analyses examined associations between the Suppress findings and clinical features of the 19 OCD patients. Using Spearman rank correlation, there was a trend toward correlation between the doubt/checking symptom dimension and RT on Valid Suppress trials ($p < 0.07$; $\rho = .43$), with increased doubt/checking correlating with increased RT (Fig. 4a). There was also a significant correlation between increased doubt/checking and decreased accuracy on Valid Suppress trials ($p < 0.04$; $\rho = -.50$) (Fig. 4b). However, significant correlations were not observed on the higher working memory load Lure

Suppress trials for either RTs or accuracy (all $p > 0.2$), suggesting normal working memory performance in the doubt/checking subgroup (see Discussion below). No significant correlations were observed between any of the other four symptom dimensions (hoarding, contamination/cleaning, taboo thoughts, or symmetry/ordering) and RT or accuracy on any of the Suppress trials (Control, Valid, or Lure) (all $p > 0.3$) (Fig. 4c). Finally, there was a positive correlation between increased Hamilton Depression scores and increased RT on high working memory load Lure Suppress trials ($p < .06$), but no correlations with RT on Control or Valid Suppress trials, or accuracy in any Trial Type (all $p > .13$).

4. Discussion

4.1. Assessing working memory in OCD

The experiments described above were framed by two important questions in the OCD field. First, do OCD patients have disturbances in working memory? Second, if there are working memory deficits in OCD, what is their relationship to OCD symptoms? Using the Ignore-Suppress task, which has increased difficulty/task-load compared to classic digit-span tasks, we did not find significant verbal working memory deficits in patients with OCD when compared to healthy controls. These data are consistent with a recent meta-analysis, which indicated that although OCD patients had impaired performance compared to healthy controls on both spatial and verbal working memory tasks across multiple studies, the effect size was small and clinically-insignificant ($\sim 1/3$ of a standard deviation worse than controls) (Abramovitch et al., 2013).

These results contribute to a growing body of literature indicating that people with OCD do not in general demonstrate verbal working memory deficits. Compared to other studies that have previously addressed this question, our paradigm requires an increased working memory load, since participants needed to store 6 unrelated words as well as their associated colors in working memory. Thus, even when the memory load is significantly increased, OCD subjects perform like healthy controls. These results contrast with those from people with schizophrenia, who demonstrate clear deficits on this task (Eich et al., 2014; Smith et al., 2011). Performance on working memory tasks like this one may therefore serve as an objective way to dissociate these two disorders (Abbruzzese, Ferri, & Scarone, 1997; Cavallaro et al., 2003).

In addition to increasing the memory load compared to prior studies assessing verbal working memory, we also eliminated several other confounds that could potentially impact the measurement of working memory. First, we only tested unmedicated OCD patients. In fact, many patients were medication-naïve, and all were medication-free for at least 4 months prior to testing. This may be an important factor, as many medications, particularly those with GABAergic, anticholinergic or antihistaminergic effects, can impact either memory capacity or performance on memory-related tasks (Tannenbaum, Paquette, Hilmer, Holroyd-Leduc, & Carnahan, 2012). Second, OCD patients were free of co-morbid depression, a condition that can independently lead to neurocognitive deficits (Chamberlain & Sahakian, 2006; Lee, Hermens, Porter, & Redoblado-Hodge, 2012). Finally, all testing in female subjects was performed at the same stage in the menstrual cycle, since hormonal status can have an impact on working memory performance (Hampson & Morley, 2013).

4.2. Is repetitive checking related to working memory deficits?

Several theories have been proposed suggesting that repetitive checking behaviors emerge because OCD patients have ‘forgotten’ if they have correctly performed a particular action. This has been a particularly popular theory for the emergence of checking behaviors to prevent feared outcomes, such as checking to make sure a stove has been turned off or a door has been locked. However, evidence from the literature indicates that patients with these types of compulsions continue to check *despite* accurately remembering that they have performed the action in question, consistent with normal working memory (MacDonald, Antony, Macleod, & Richter, 1997; Tolin et al., 2001; van den Hout & Kindt, 2003). Though our data and that of others suggest that a necessary prerequisite for this explanatory model of the evolution of repetitive behaviors in OCD – i.e., the presence of *clinically-significant* working memory deficits – is not broadly present (Abramovitch et al., 2013), an alternative possibility is that working memory abnormalities may be more prominent in OCD patients with predominant checking compulsions. This theory receives some support from our exploratory clinical correlations, with the important caveat that there is a risk of false positive findings in our sample due to the exploratory nature of these analyses. Specifically, we observed a correlation between the doubt/checking symptom dimension and decreased accuracy on the Valid Suppress trials, as well as a trend towards increased reaction times. Though this suggests that patients with prominent doubt/checking symptoms are more likely to doubt performance, paradoxically this was not the case in the higher working memory load Lure Suppress trials, suggesting that the problem does not directly stem from a working memory deficit. Thus, it is possible that checking compulsions in OCD patients stem from deficits in other functional domains, such as lack of memory confidence leading to patients mistrusting memories that they know are accurate (MacDonald et al., 1997; Tolin et al., 2001; van den Hout & Kindt, 2003). Interestingly, several studies have suggested that repeated checking directly decreases memory confidence, even in healthy controls, which may give hints about the origin of compulsive checking (Giele et al., 2013; Harkin & Kessler, 2009; Harkin & Kessler, 2011; Harkin, Rutherford, & Kessler, 2011; van den Hout & Kindt, 2004). Other factors that may contribute to the evolution of checking compulsions include feelings of incompleteness, doubt, and uncertainty (Jacoby, Fabricant, Leonard, Riemann, & Abramowitz, 2013; Tolin, Abramowitz, Brigidi, & Foa, 2003); increased salience of imagined feared outcomes (Psychometri, 2005; Salkovskis, 1985); and/or overestimation of the likelihood of occurrence of feared events (Cisler & Koster, 2010; Jones & Menzies, 1997; Jones & Menzies, 1998; Moritz & Jelinek, 2009). These possibilities will serve as hypotheses for future studies.

4.3. Alternative interpretations

Though our findings suggest that working memory dysfunction does not contribute to OCD symptomatology, several study limitations prevent us from definitively ruling out this possibility. First, it is possible that deficits would have been observed on a task with an even higher memory load (e.g. 8- or 10-item task), since we observed a ceiling effect for accuracy. This idea is supported by Chamberlain et al. (2007), who observed spatial working memory deficits on hard, but not easy, difficulty levels in the CANTAB spatial working memory task. Second, although we found no group differences in behavioral performance

on this task, it is possible that maintaining normal working memory processes took other cognitive resources offline and/or led to abnormal compensatory functioning in other areas of the brain, as can be seen both in working memory and in reversal learning tasks in OCD patients (Chamberlain et al., 2008; Henseler et al., 2008; Remijnse et al., 2006; Remijnse et al., 2009). However, we did not perform simultaneous functional imaging, and therefore could not assess this possibility. In addition, particular subgroups of OCD patients, such as those with predominant checking symptoms, might demonstrate working memory deficits that could not be observed in a mixed OCD population such as the one in our study. Finally, it is possible that spatial working memory tasks are more relevant to OCD checking compulsions than the verbal working memory task employed in this study; however, notably, observed effect sizes in spatial working memory tasks are also small according to a recent meta-analysis (Abramovitch et al., 2013).

Another possibility is that there is an interaction between working memory processes and anxiety levels in OCD, and that working memory deficits might therefore emerge in OCD patients under conditions of high anxiety and stress. In fact, this could be a generalizable property related to cognitive functions in OCD, and is supported by findings in the literature indicating that anxiety levels can affect cognitive status (Bishop, 2007, 2009; Deckersbach, Moshier, Tuschen-Caffier, & Otto, 2011). Although OCD is no longer categorized as an anxiety disorder in DSM-5, it is clear that in many cases obsessions are associated with significant anxiety, and compulsive behaviors result in a temporary decrease in anxiety levels. Likewise, there are reported cases of trauma-associated OCD, and indications that increased anxiety levels can lead to symptom exacerbations in OCD patients (Fostick, Nacasch, & Zohar, 2012; Lafleur et al., 2011; Pitman, 1993; Real et al., 2011; Sasson et al., 2005). It is therefore possible that the generation and maintenance of abnormal repetitive behaviors is linked to interactions between cortico-basal ganglia circuits and amygdala and/or ventral hippocampal nodes. Since anxiety measures were not performed in our study on the day of testing, our ability to determine if OCD patients were anxious during this working memory test was limited. However, future studies may be able to dissect the contributions of anxiety to impaired neurocognitive functioning in OCD by (1) using tasks geared to trigger symptom exacerbations (i.e. using symptom-relevant words in the Ignore-Suppress task); and (2) monitoring anxiety and stress levels online during task administration via skin conductance and salivary cortisol assays. This would allow us to directly test the theory that cognitive impairment emerges as anxiety levels increase.

4.4. Investigating neurocognitive function in psychiatric illness

As described in the Introduction, the question of whether there are working memory deficits in OCD has been an area of debate, because there has been significant variation in findings across multiple studies. The challenges of studying working memory in OCD patients highlight a larger issue in the field-how do we rigorously investigate neurocognitive function in psychiatric illness with consistency across multiple sites? As discussed in both meta-analyses and a recent review (Abramovitch et al., 2013; Harkin & Kessler, 2011; Shin et al., 2013), discrepancies in the literature abound, and are attributable to a variety of factors. These issues are broadly relevant to the study of neurocognitive function in psychiatric illness, and are discussed in detail below.

4.4.1. Challenge 1: Several conditions; one disease category—One of the biggest challenges currently facing psychiatric research is that heterogeneous conditions are often pooled into a single disease category, making it difficult to establish unified neurocognitive findings. For example, in OCD, there appear to be subcategories within the diagnosis that may have different underlying neurobiology and treatment response, such as tic-related OCD (Eichstedt & Arnold, 2001; Leckman, Bloch, & King, 2009; Leckman & et al., 2010) and pediatric-onset OCD (Eichstedt & Arnold, 2001; Hanna et al., 2012; Kalra & Swedo, 2009; Leckman et al., 2009; Maia, Cooney, & Peterson, 2008). It has also been suggested that different OCD subdomains (i.e. contamination/cleaning; harm/checking; symmetry/ordering; aggressive/sexual; hoarding) may have different neurobiologic underpinnings, and people with different symptom types may therefore perform differently on neurocognitive tasks (Leckman et al., 2010; Mataix-Cols, Rosario-Campos, & Leckman, 2005; Mataix-Cols & et al., 2004). This is particularly well-established for primary hoarding, which has been recognized as a separate disorder in DSM-5 in an attempt to address this problem (Mataix-Cols et al., 2010; Saxena, 2007; Tolin, Witt, & Stevens, 2014). However, the issue of heterogeneity is not limited to OCD and related disorders. Another classic example is the presence of ‘typical’ and ‘atypical’ depression within the category of major depressive disorder, despite the fact that these subtypes have very different symptom presentations (Schmidt, Shelton, & Duman, 2011; van Loo, de Jonge, Romeijn, Kessler, & Schoevers, 2012). Thus, sampling from different disease subpopulations may account for discrepancies between studies.

A new NIMH-sponsored initiative called RDoC (Research Domain Criteria) (Casey & et al., 2013) attempts to address this issue by defining neurocognitive constructs that cut across diagnostic categories. For example, there is evidence that working memory is impaired in multiple disorders including schizophrenia (Barch & Ceaser, 2012; Barch & Smith, 2008; Volk & Lewis, 2010; Young, Powell, Risbrough, Marston, & Geyer, 2009) and ADHD (Alderson et al., 2013; Doyle, 2006; Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005), which may be indicative of shared neural dysfunction between these two distinct disease categories. By identifying genetic and neural circuit abnormalities leading to working memory deficits independent of disease category, we may ultimately be able to develop treatments that target this domain irrespective of neuropsychiatric diagnosis.

4.4.2. Challenge 2: Too many tasks in the kitchen?—An additional challenge limiting the field’s ability to definitively conclude if specific neurocognitive abnormalities are present in defined patient populations is that different task variants are used across multiple sites. Even small changes in task parameters can lead to behavioral differences, and large differences are often present in tasks that are purportedly measuring the same constructs. For example, stop-signal reaction time tasks that are used to assess response inhibition in many neuropsychiatric illnesses, including OCD, vary in multiple parameters including trial number, block number, and the type of stop-signal (auditory vs. visual) (Hughes, Johnston, Fulham, Budd, & Michie, 2013; Sylwan, 2004; Verbruggen, Chambers, & Logan, 2013). Not surprisingly, results vary in both healthy subjects and in OCD patients depending on the specific parameters chosen (Leotti & Wager, 2010) (unpublished data), since slightly different neurocognitive functions are likely being tested. For example, if

subjects are verbally encouraged to optimize speed vs accuracy, performance on response inhibition tasks changes dramatically (Leotti & Wager, 2010).

To address this issue, attempts have been made to achieve consensus on which tasks should be used to investigate particular neurocognitive functions. This effort is exemplified by the MATRICS Consensus Cognitive Battery, which was developed collaboratively by an international consortium of researchers to enable standardized assessment of treatments for neurocognitive enhancement in schizophrenia (Kern et al., 2008; Nuechterlein et al., 2008); another ongoing project stemming from the MATRICS initiative is CNTRICS (Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia). Key factors in the development of consensus included initial broad committee review of candidate tests, expert panel review of the most promising measures, selection of a beta-test battery, and choice of final tests following repeated administration to a large group of participants with schizophrenia. Importantly, panel members recused themselves from assessing tasks that they had a personal role in creating due to potential conflict of interest. Such committees could also be used to identify gaps that need to be filled by the creation of new tasks, and could even play a role in the consensus development of new tests. To encourage use of this type of strategy, national funding agencies could consider making validated consensus batteries freely available to funded investigators, as is currently being done via the NIH Toolbox Program until at least July 2014 (<http://www.nihtoolbox.org/Pages/default.aspx>). In a similar effort, the Penn Computerized Neurocognitive Battery is freely available to qualified researchers (https://www.med.upenn.edu/bbl/bbl_cnb.shtml).

4.4.3. Challenge 3: You say tomato, I say tomahto—A related challenge is inter-site variability in task administration. Even if standardized tasks are used, variation in subject instruction can lead to significant differences in task performance (Leotti & Wager, 2010). For example, verbal feedback from an encouraging task administrator vs computerized feedback may yield different results. Though individual sites attempt to minimize discrepancies by creating standardized instructions for patients, it is very difficult to control for differences in patient comfort with particular staff members leading to different levels of compliance on tests of cognitive control. In addition, journal word limits can make it difficult to convey all potentially pertinent details regarding subject instruction.

Several possible solutions to this problem exist. First, in this era of inexpensive data storage, fully-detailed online supplementary methods could be standard procedure for all journals. In addition, submission of detailed videos of task administration to platforms such as JoVE (Journal of Visualized Results), or addition of such videos to the online supplement of traditional journals, should be considered. Collaboration between groups towards these efforts should be strongly encouraged, since cooperation to maximize standardization is necessary to move the field forward.

4.4.4. Challenge 4: State vs. trait—As discussed above in relationship to working memory assessment in OCD, complex symptom clusters may be playing a significant role in generating neurocognitive abnormalities in neuropsychiatric disorders. These state differences may lead to discrepancies in studies both within and between sites. For example, increased anxiety levels have been linked to decreased cognitive performance in working

memory and spatial navigation (though notably, anxiety may lead to improvements in some measures of intentional control) (Robinson, Vytal, Cornwell, & Grillon, 2013). However, these levels are not routinely recorded by self-report in studies that are not primarily investigating anxiety, and typically are not quantitatively assessed via skin conductance or cortisol assays even in studies whose focus is anxiety.

Differences in emotional state could lead to impaired cognitive performance through a variety of mechanisms. For example, acute increases in anxiety and obsessive thoughts can lead to decreased attention, and therefore contribute to generalized difficulties across multiple neurocognitive tasks (Armstrong & Olatunji, 2012; Harkin & Kessler, 2009; Harle, Shenoy, & Paulus, 2013). Similarly, subclinical levels of depression can lead to generalized impairments due to decreased incentive motivation (Der-Avakian & Markou, 2012). In another example, fear leads to enhanced activation of prefrontal-cingulate circuits, which may take prefrontal cortex offline for participation in other higher level executive functions. Finally, temporary circuit hypoactivation resulting from active symptoms may lead to corresponding decreases in functions subserved by those circuits, while these functions may be perfectly normal in the absence of symptoms (Pessoa, 2009).

Controlling for differences in emotional state both within and across sites is a very difficult prospect. It is neither practical nor feasible to quantitatively assess anxiety and stress levels in all neurocognitive studies. However, we recommend that investigators consistently include standardized self-report measures of relevant symptom domains when performing neurocognitive assessments.

4.4.5. Conclusion: A clear path?—Neurocognitive research in OCD has been plagued by lack of consistency in results, which contrasts with the relative convergence of findings from structural and functional imaging studies identifying abnormal neural circuits that are associated with OCD symptoms. As described above, the reasons for discrepancies between studies are likely multi-factorial. In order to advance our understanding of OCD, it is essential to identify neurobehavioral probes that reliably reveal the domains of neural dysfunction in patients. As mentioned in the introduction, clearly-defined cognitive endophenotypes have significant utility for both the construction of new animal models using novel technologies, and the validation of translational significance of existing animal models. Molecular and cellular dysfunction underlying neurocognitive abnormalities relevant to the human condition can then be identified, as a first step towards identifying new treatment targets. To achieve this goal, it is crucial that we as a field first work together to develop consensus regarding task development and administration. This goal is crucial not only for OCD and anxiety research, but for neuropsychiatric research in general. Consortia such as MATRICS and CNTRICS may serve as a model for future efforts, so that we can maximize our collective intellectual resources in this era of great promise to develop new treatment approaches.

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Figure 1.

Ignore-Suppress Task Methodology. In Ignore (A), an instruction to Attend to either the red or blue words appeared followed 1 s later by a 6-word memory-set for 4.5 s, followed 3 s later by a probe word. In Suppress (B), the 6-word memory-set appeared for 4.5 s, followed 1 s later by an instruction to Remember only the words of one color (red or blue). This was followed 3 s later by a probe word. In both Ignore and Suppress, a “Yes” response to the probe was required if the probe word matched one of the words that was supposed to be in working memory, and a “No” response was required otherwise.

Figure 2.

Ignore-Suppress Reaction Times. Box and whisker plots showing reaction time data (for correct trials only) on the three different trial types (Control, Lure, Valid) for Healthy Controls (HC) and OCD subjects (OCD), separately for the Ignore and Suppress tasks. Participants were significantly slower in the Suppress condition as compared to the Ignore condition (936.03 vs. 745.45 ms, respectively) ($p < .001$), and were significantly slower in the Lure trials (917.61 ms) than in both the Control (797.87 ms) and Valid (806.74 ms) trials ($p < .001$). The interaction between Condition and Trial Type was significant (in Ignore: Control = 732.36; Lure = 765.59; Valid = 738.39; in Suppress: Control = 863.39; Lure = 1069.62; Valid = 875.09) ($p < .001$). However, the main effect of Group was not significant, nor were any of the other interactions (Group $\times$ Condition; Group $\times$ Trial Type; Condition $\times$ Trial Type $\times$ Group) (all F s < 1.1).

Figure 3.

Ignore-Suppress Accuracy. Box and whisker plots showing accuracy (percent correct) on the three different trial types (Control, Lure, Valid) for Healthy Controls (HC) and OCD participants (OCD), separately for the Ignore and Suppress conditions. Participants were significantly more accurate in Ignore than in Suppress (96.02% vs. 89.32%, respectively) ($p < .001$). However, the main effect of Group was not significant (HC: 93.17%; OCD: 92.16%), nor was the main effect of Trial Type (Control: 94.05%; Lure: 91.27%; Valid: 92.68%), nor were any of the interactions (Group $\times$ Condition; Group $\times$ Trial Type; Condition $\times$ Trial Type; Condition $\times$ Trial Type $\times$ Group).

Figure 4.

Exploratory Clinical Correlations. (A) Scatter-plot demonstrates positive correlation of increased doubt/checking with RT on Valid Suppress trials [Spearman rank correlation: $p < 0.07$; $\rho = .43$; $r^2 = .248$]. (B) Scatter-plot demonstrates negative correlation of increased doubt/checking with accuracy on Valid Suppress trials [Spearman rank correlation: $p < 0.04$; $\rho = -.50$; $r^2 = .039$]. (C) Scatter-plots demonstrate no significant correlations between

hoarding, contamination/cleaning, taboo thoughts, or symmetry/ordering and RT on Valid Suppress trials (all $p > 0.3$).

Table 1

Demographics and clinical characteristics. Demographic, clinical, and neuropsychological characteristics of Healthy Controls and OCD participants. Groups were matched on age, gender, ethno-racial groups, and verbal IQ.

Demographics and clinical characteristics		Healthy controls <i>n</i> = 23	OCD subjects <i>n</i> = 19
Age (SD)		30.0 (8.0)	32.1 (9.4)
Sex	Male	12	10
	Female	11	9
Ethnicity	African-American	0	1
	Asian	3	2
	Hispanic	2	1
	Caucasian	18	15
YBOCS		0	27.7 (4.3)
HAM-D		0.3 (0.6)	5.6 (3.8)
Lifetime history of tics		0	1
Age of initial OCD diagnosis		N/A	16.4 (6.7)
DSM-IV Axis I psychiatric comorbidity	No current or past comorbidity	23	12
	Current/past MDD	0/0	0/7
	Current social phobia	0	1
	Current panic disorder	0	1
	Current GAD	0	1
	Current tic disorder	0	1
Family History of OCD		0	5

Table 2

Signal Detection Theory measures for Healthy Controls and OCD subjects. No significant differences were found in any measure, indicating equivalent performance of Healthy Controls (HC) and OCD participants in the Ignore and Suppress conditions.

Measure	Healthy controls		OCD subjects	
	Mean	SD	Mean	SD
Hit rate	0.93	0.05	0.92	0.07
False alarm rate	0.07	0.05	0.08	0.06
Criterion C	0.05	0.66	-0.02	0.79
d'	3.16	0.65	3.17	0.88