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Cognitive inflexibility in obsessive-compulsive disorder

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Abstract

Obsessive-Compulsive Disorder (OCD) is characterized by maladaptive patterns of repetitive, inflexible cognition and behavior that suggest a lack of cognitive flexibility. Consistent with this clinical observation, many neurocognitive studies suggest behavioral and neurobiological abnormalities in cognitive flexibility in individuals with OCD. Meta-analytic reviews support a pattern of cognitive inflexibility, with effect sizes generally in the medium range. Heterogeneity in assessments and the way underlying constructs have been operationalized point to the need for better standardization across studies, as well as more refined overarching models of cognitive flexibility and executive function. Neuropsychological assessments of cognitive flexibility include measures of attentional set shifting, reversal and alternation, cued task switching paradigms, cognitive control measures such as the Trail-Making and Stroop tasks, and several measures of motor inhibition. Differences in the cognitive constructs and neural substrates associated with these measures suggest that performance within these different domains should be examined separately. Additional factors, such as the number of consistent trials prior to a shift and whether a shift is explicitly signaled or must be inferred from a change in reward contingencies, may influence performance, and thus mask or accentuate deficits. Several studies have described abnormalities in neural activation in the absence of differences in behavioral performance, suggesting that our behavioral probes may not be adequately sensitive, but also offering important insights into potential compensatory processes. The fact that deficits of moderate effect size are seen across a broad range of classic neuropsychological tests in OCD presents a conceptual challenge, as clinical symptomatology suggests greater specificity. Traditional cognitive probes may not be sufficient to delineate specific domains of deficit in this and other neuropsychiatric disorders; a new generation of behavioral tasks that test more specific underlying constructs, supplemented by neuroimaging to provide greater insight into the underlying processes, may be needed.

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Cognitive inflexibility in OCD: face validity and conceptual challenges

Obsessive-Compulsive Disorder (OCD) is characterized by maladaptive patterns of repetitive, inflexible cognition and behavior. Clinically, individuals with OCD have difficulty shifting between mental processes to generate adaptive behavioral responses, especially in the context of their symptoms. In keeping with this, many neurocognitive studies suggest abnormalities in cognitive flexibility in individuals with OCD (e.g. Remijnse et al., 2006, Chamberlain et al., 2007, Chamberlain et al., 2008, Gu et al., 2008, Viswanath et al., 2009). However, not all studies have found abnormalities (e.g. Moritz et al., 2009); and when abnormalities are detected, they are not always consistent across studies.

One critical source of inconsistency may be variability in defining and operationalizing the construct of cognitive flexibility (Dajani and Uddin, 2015). Cognitive flexibility has been broadly defined as the ability to flexibly adjust behavior to the demands of a changing environment (e.g. Armbruster et al, 2012; Dajani and Uddin, 2015), more narrowly as relating only to tests of attentional set shifting and task shifting (as further defined below; Dajani and Uddin, 2015), and in numerous other way. One thing that is clear is that cognitive flexibility, however it is operationalized, depends on the interaction of multiple component cognitive systems. It has been conceptualized as an emergent property of efficient executive function (EF) and as depending on, at least, component systems subserving salience detection, attention, working memory, and inhibition (Dajani and Uddin, 2015).

In the OCD literature, aspects of cognitive flexibility have been probed using several different categories of task, including set shifting, reversal learning, cued task switching, and tests of cognitive or motor inhibition. These specific tasks vary in which specific cognitive constructs and which underlying EF subsystems they probe (Table 1). For example, the Wisconsin Card Sorting Test (WCST) and the Object Alternation Test (OAT) both require flexibility, but the WCST tests the ability to deviate from a behavioral response that has been repeatedly reinforced, while the OAT tests the ability to repeatedly alternate between behaviors in the absence of a repeated response. Even when the tests utilized are quite similar, outcome measures may differ between studies, as may practical issues during administration. For example, some fMRI studies have participants practice measures ahead of time in order to eliminate behavioral differences during scanning (e.g. Chamberlain et al., 2008), whereas others do not. Such methodological differences make it challenging to compare across studies and reduce the ability of meta-analytic approaches to detect subtle neurocognitive deficits.

Most tests used in traditional neuropsychological assessments (such as the WCST) were originally developed to assess gross deficits in cognitive functioning, such as those following frontal excisions and brain lesions (Reitan and Wolfson, 1994, Eling et al., 2008), and not the more subtle deficits that may characterize psychological and neurodevelopmental disorders. Cognitive processes tend to be interdependent, and so performance on a particular task will inevitably include systematic variance attributable to a range of processes beyond the one that is purportedly being assessed. This may be particularly true of a high-level process like cognitive flexibility (Dajani and Uddin, 2015). This has been termed the ‘task impurity’ problem (Hughes and Graham, 2002). There may be advantages to using complex

tasks that tap into multiple underlying abilities, especially in clinical settings, as they often have ecological validity (Snyder et al, 2015); but from the perspective of dissecting underlying mechanisms and identifying circumscribed deficits such tasks are problematic. Newer measures are designed to assess constructs such as goal-directed versus habitual control with greater specificity (Daw et al., 2011, Gillan et al., 2011, Gillan et al., 2014b), but they still depend on other neurocognitive capacities, such as attention and working memory. It is to be hoped that the careful characterization of deficits using hypothesis-driven approaches will help us to better understand some of the older literature, through careful consideration of the relationships of the constructs assessed.

Many studies over three decades have examined neuropsychological function in OCD using standard test batteries. Several recent meta-analyses have provided valuable syntheses of these studies. Overall they support a pattern of cognitive inflexibility in OCD, with variable effect sizes, generally in the medium range (Abramovitch et al., 2013, Shin et al., 2013, Snyder et al., 2015). The latter two of these report effect sizes for individual tasks, not just broad constructs – the construct of cognitive flexibility has been variably operationalized, and relying of findings at the construct level can therefore be problelmatic. They used different approaches to the analysis of studies of executive function (EF), and of set shifting in particular. Cognitive deficits in other domains have also been identified, leading some authors to conclude that OCD is associated with broad but nonspecific impairments in executive function (Abramovitch et al., 2013, Snyder et al., 2015). Substantial heterogeneity in this literature has made drawing more specific conclusions difficult. It should be noted that these large meta-analytic reviews , which included 88 (Shin et al., 2013) and 110 studies (Snyder et al., 2015) each, summarize overlapping literatures, and thus cannot be considered independent; nevertheless, consistency between the two, given that they used different methodologies, is reassuring.

Here we review studies of processes of relevance to cognitive inflexibility in OCD, seeking to identify common themes in which we can have confidence, as well as areas of discrepancy in the extant literature. We have chosen to discuss a range of tasks that have been studied in this context in OCD, rather than focusing on a narrower definition of cognitive flexibility to constrain the material discussed. A narrower definition might include a subset of these tasks (for example, following Dajani and Uddin 2015, of only set shifting and task switching). Conversely, a broader selection of tasks might be included, such as those involving various aspects of learning and memory, upon which instances of cognitive flexibility must often rely in practice. We have focused on tasks and constructs that have been studied in the context of inflexibility in OCD in the existing literature.

This focus of this review on OCD merits comment. It is broadly accepted that such categorical diagnoses are provisional constructs at best, and not systematically related to underlying pathophysiology. The nature, definitions, and boundaries of our diagnoses are likely to evolve as our understanding of the underlying psychological constructs and brain biology advances, and excessively reifying current diagnostic categories is treacherous. As a corollary, even if an explanatory framework such as ‘impaired cognitive flexibility’ proves to be useful for the understanding of patients with a diagnosis of OCD (or a subset thereof), it is unlikely to be specific to these patients; it is more likely to be a transdiagnostic trait and to

also occur in patients with related diagnoses (see Gillan et al, 2016, for an example of such a transdiagnostic analysis).

Despite this, a focus on OCD (as traditionally defined) is both unavoidable and useful. It is unavoidable because the large majority of the literature is organized around such diagnostic entities. It remains useful, from a clinical perspective, because patients continue to present with such categorical diagnoses, and the diagnoses are accurate descriptions of many (which is why they have been adopted by clinicians over time). Organizing studies of cognition around existing categories helps to deploy them to explain patient phenomenology. It is to be hoped that future advances will help us to refine diagnostic categories (or dimensions), and that over time they will come to more cleanly correspond to well-validated constructs from cognitive psychology, neurobiology, and other disciplines. In the current review, however, we accept the diagnostic organization of the literature as it exists, rather than as we hope it one day will be.

Experimental probes of cognitive flexibility

Cognitive flexibility is a complex construct; it has been variably defined in the literature and has been operationalized using a variety of tasks. Characteristics of tasks that have been examined in individuals with OCD and that are included in this review are given in Table 1.

Cognitive flexibility has been characterized as an emergent property arising out of efficient executive function (e.g. Dajani and Uddin, 2015). As such, it relates to numerous underlying constructs; deficits in cognitive flexibility may arise in different ways, from deficiency in one or another of these underlying systems, or in their interactions. Different behavioral probes are likely tap into different aspects of this complex process.

Friedman and Miyake (2000) developed a framework, the unity/diversity model, describing the processes that underlie EF; this was explicitly adopted in a recent meta-analysis of studies of EF in OCD (Snyder et al, 2015). Because cognitive flexibility emerges out of the efficient functioning of EF systems, this framework provides a useful organizing scheme. As a corollary, cognitive inflexibility may result from dysfunction in any of several components of this EF framework. EF is proposed to include several separable but interrelated processes – updating working memory, shifting, and inhibition – together with the shared capacity to maintain a representation of goal and context, and to monitor and update this representation. It might be argued that within this framework shifting is most closely related to cognitive flexibility (Dajani and Uddin, 2015). But in practice, cognitive inflexibility can result from deficits in a range of EF subcomponents, as further detailed below.

Cognitive inflexibility in OCD: attentional set shifting

Attentional set shifting is the “ability to switch attention from one aspect of a stimulus to another in an ongoing task, in accordance with changing reinforcement contingencies” (Chamberlain et al., 2005). Efficient set shifting is a core aspect of cognitive flexibility (Dajani and Uddin, 2015). There are several different types of set shifting, which appear to be associated with distinct neural substrates. These are generally defined within the context

of simple discrimination tasks in which the rules determining which option is 'correct' evolve over time and are signaled by feedback.

Attentional set shifting can be further broken down into *intradimensional* and *extradimensional set shifting*. An intradimensional (ID) shift is one in which the type of rule being followed does not change, but the specific instance of that rule does – for example, when color remains the salient characteristic of the stimulus, but the reinforced option in a discrimination task switches from red to yellow. An extradimensional (ED) shift in a discrimination task refers to a shift in which the salient characteristic switches to a different aspect of the stimuli – for example, when the color of the stimuli ceases to be informative and the shape becomes the discriminating characteristic. In general, ED shifts are associated with higher cognitive demand/greater cost (in reaction time, for example) than ID shifts (Oh et al., 2014). Intradimensional and extradimensional shifts are most clearly probed using the Intradimensional/ Extradimensional Shift Task (IED) from the Cambridge Neuropsychological Test Automated Battery (CANTAB)(Sahakian and Owen, 1992). Attentional set shifting is also probed by the Wisconsin Card Sort Task (WCST).

Measures of attentional set shifting have fairly consistently revealed deficits in OCD, with medium effect sizes (although there is some controversy in the literature as to the presence and importance of these deficits; e.g. Abramovitch et al, 2015). Meta-analyses have reported increased perseverative errors on the WCST: (g=−.51; k=21)(Shin et al., 2013) and (d=.44; k=42)(Snyder et al., 2015). Interestingly, significantly larger effects have been reported with a computerized version of the WCST than with the classic manual version (Shin et al., 2013). Different neuropsychological profiles on the WCST have been demonstrated for OCD patients with and without a history of tics (Gruner and McKay, 2013).

Meta-analyses of performance on the IED in OCD have been more variable but are also indicative of attentional set shifting deficits. One meta-analytic review reported the ID and ED trial scores separately and demonstrated a significant deficit for ID shifting [g=−.37; k=5, p=.004)], with a weaker and nonsignificant effect on ED shifting [g=−.31; k=6, p=.068) (Shin et al., 2013). Another review reported a significant deficit in the overall accuracy of shifting in the IED (d=.50; k=7, p=<.001) (Snyder et al., 2015), without breaking down the different types of shift. Deficits in attentional set shifting have been identified in unaffected first-degree relatives of probands with OCD, suggesting that these deficits may represent a cognitive endophenotype (Chamberlain et al., 2007).

Cognitive inflexibility in OCD: reversal learning

Reversal learning also requires shifting from one stimulus to another based on feedback. In this casel, however, shifts relate to entire composite stimuli, rather than to individual stimulus attributes. Reversal learning occurs when a stimulus that was previously neutral becomes salient, or when a stimulus that was previously rewarded becomes neutral. Reversal-specific learning is associated with activation of the lateral orbitofrontal cortex (OFC) (Ghahremani et al., 2010). Neurobiological factors that influence reversal learning do not necessarily affect extra-dimensional or intra-dimensional shifting. For instance, prefrontal serotonin depletion in marmoset monkeys significantly impairs reversal learning,

but not attentional set shifting (Clarke et al., 2005). By definition, reversal learning can only occur after stimuli have been associated with reward. This association can be reliable or probabilistic. *Probabilistic learning* refers to situations where the association between response and reward is more uncertain and rewarded intermittently (e.g. occurs 75% of the time). Thus, the same response to the same stimulus can result in different outcomes on different trials (Helie et al., 2013). Reversal of probabilistic associations typically requires more trials, as individual unrewarded trials are not *prima faciae* evidence that reinforcement contingencies have changed.

In reversal tasks, as in attentional set-shifting tasks, a change in task contingencies is not explicitly signaled to the subject but must be inferred from feedback. An important parameter in any such task is the number of consistent trials prior to a shift. More consistent trials before a shift tend to make a response pattern more automatic or 'prepotent' and therefore to make shifts more difficult (i.e. they reduce flexibility); difficulty inhibiting prepotent responses may be a hallmark of certain forms of psychopathology. Studies and tasks used to characterize set shifting vary substantially in this way. In the OAT and the DAT, optimal performance requires shifting what is chosen on every trial. In the WCST, rules are typically changed after 10 correct responses; in the IED, the change typically happens after 6 correct responses.

Reversal learning paradigms tend to be less standardized across studies than measures of attentional set shifting and are thus more difficult to meta-analyze. Overall, studies of reversal learning have not revealed consistent behavioral differences in reversal-related errors in individuals with OCD compared to controls, although there may be more subtle performance abnormalities (Remijnse et al., 2006, Chamberlain et al., 2008, Valerius et al., 2008). Behavioral overtraining, which is sometimes done to minimize performance differences in neuroimaging studies (Chamberlain et al., 2008), may mask subtle differences that could emerge early during training or under conditions of high cognitive load; careful parametric exploration of these issues has yet to be done.

Neuroimaging during reversal learning has revealed differences in brain activation, despite normal performance, with OCD patients underactivating prefrontal regions including the OFC (Remijnse et al., 2006, Chamberlain et al., 2008). Decreased responsiveness in the right caudate has also been noted in patients on rewarded trials (Remijnse et al., 2006). Decreased prefrontal activation has been noted in unaffected healthy relatives of probands, suggesting that inefficiency in this circuitry may be an endophenotype for the disorder (Chamberlain et al., 2008).

The presence of neural abnormalities in the absence of differences in performance suggests that standard behavioral probes may miss important deficits. Subjects with OCD may be able to compensate for underlying abnormalites and perform within normal limits despite the presence of underlying neural inefficiency. Such abnormalities may become behaviorally apparent when cognitve demand increases, as this may overwhelm subjects' ability to compensate. In the real world, individuals are often subjected to distraction, cognitive load, and competing demands, and thus deficits that emerge only in the presence of such demands may have significant ecological validity. As noted above, subtle behavioral differences have

been reported in reversal learning studies: OCD patients have been reported to make more spontaneous errors overall, irrespective of reversal (Remijnse et al., 2006); and unaffected first degree relatives have been reported to have slower response times (Chamberlain et al., 2008). Such behavioral measures may be more sensitive to underlying deficits than the standard behavioral index of errors after reversal and may be required to detect abnormalites in these tasks.

Comparison across studies of reversal learning in OCD, using both behavioral and neural outcomes, would be facilitated by greater standardization. For example, some studies have sought to capture a change in behavior after reversal (Chamberlain et al., 2008), while others have modeled learning that takes place immediately prior to the behavioral change (i.e. the last false response after a contingency change, prior to a shift in behavior) (Remijnse et al., 2006). These are both interesting questions, but the differing focus renders generalization of the nature of any underlying deficits difficult. In light of this discussion, we suggest that both trials before a reversal (and thus prepotency) and cognitive load be parametrically varied wherever possible, and that trial-by-trial analyses immediately following a change in contingencies examine both failures and successes.

Cognitive inflexibility in OCD: alternation tasks

In object alternation (OAT) and delayed alternation (DAT) tasks, shifts are performed on every trial. In the OAT, optimal performance requires selecting a different stimulus on every trial – that is, avoiding repeatedly selecting the same stimulus. The DAT is similar except that optimal performance requires alternation between targets at different points in space.

Patients with OCD have been found to have deficits in the OAT and DAT, with some consistency, though effect sizes have varied across studies. Two published meta-analyses have examined these two tests separately from other measures of cognitive flexibility or executive function. One reported significantly more perseverative errors in OCD patients than in controls (g=−.48; k=5)(Shin et al., 2013). The other, which included more studies, reported decreased accuracy scores in OCD patients than controls (d=.32; k=17) (Snyder et al., 2015). Unaffected siblings of OCD probands have also been shown to have deficits in the OAT in a single study, leading to the suggestion that the deficit may be an endophenotype for OCD (Viswanath et al., 2009).

Cognitive inflexibility in OCD: cued task switching

Task switching is another core aspect of cognitive flexibility (Dajani and Uddin, 2015). It describes situations in which subjects must change strategy based on an explicit instruction or cue, rather than inferring changed contingencies from the pattern of reward receipt. Task switching paradigms (Braver et al., 2003, Gu et al., 2008, Remijnse et al., 2013) typically include both task-repeat and task-switch trials; the number of consistent trials presented before a signaled task switch can be parametrically varied. Using explicit cues and representations to direct action appears to recruit different cognitive abilities and neural mechanisms (e.g. right inferior frontal gyrus and dorsal anterior cingulate) than reversal learning in response to feedback after an unsignaled change in reward contingencies (e.g.

lateral OFC) (Ghahremani et al., 2010). Task switching paradigms in healthy individuals have demonstrated that sustained cognitive control during task switching recruits the right anterior PFC, whereas transient control processes (task switch trials versus task repeat trials) recruits the left lateral PFC and left superior parietal cortex (Braver et al., 2003).

The *Trail Making Test- Part B* (TMT-B) is a complex task switching paradigm in which explicit instructions are provided and do not change over the course of the task. Subjects are presented with a distribution of letters and numbers scattered pseudorandomly across a page; they are instructed to draw a path that alternates between successive letters and numbers (i.e. A-1-B-2-C-3….). Feedback is provided when subjects make errors. TMT-B is a cognitively demanding task, requiring continuous response inhibition and attentional set shifting. (The TMT part A consists only of numbers; much less cognitive control is required.) In the TMT-B, unlike the OAT or the DAT, subjects must actively inhibit prepotent tendencies (the automatic inclination to connect numbers or letters in order, rather than alternating between the two). Motor control and constant updating of working memory are also required. However, trial and error learning is not necessary; instructions are clear, task contingencies do not change, and practice is provided at the beginning of the task.

Relatively few studies have examined cued task switching in OCD. One meta-analytic review has examined these studies and reports a deficit in individuals with OCD at trend level with a medium effect size (d=.35; k=3; p=.089) (Snyder et al., 2015). On the TMT-B, individuals with OCD have been reported to have a deficit, with consistent effect sizes across recent meta-analytic reviews: (g=−.49; k=22) (Shin et al., 2013); and (d=.54; k=37) (Snyder et al., 2015).

One task-switching study found that performance of OCD patients was more accurate but slower than that of controls, and that accuracy increased linearly with the severity of symptoms in the OCD group. This suggests that slower performance in patients represents a strategic tradeoff for the sake of accuracy (Remijnse et al., 2013).

Two studies have examined brain activation during task switching in individuals with OCD (Gu et al., 2008, Remijnse et al., 2013). One consistent finding has been reduced activation of prefrontal regions, including the orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (DLPFC), in OCD patients compared to control subjects (Gu et al., 2008, Remijnse et al., 2013). Increased activation during task switching of the left putamen, bilateral anterior cingulate cortex (ACC), and left postcentral gyrus has also been reported (Remijnse et al., 2013). Activation of the dorsal ACC and putamen correlated positively with symptom severity in the OCD group (Remijnse et al., 2013). A follow-up study showed that functional abnormalities in OCD patients on this type of task may normalize with symptom improvement and worsen with symptom exacerbation (Vriend et al., 2013), suggesting that these deficits may be state-dependent.

Cognitive inflexibility in OCD: inhibition of cognitive and motor prepotent responses

Another category of measures often examined when assessing cognitive flexibility, typified by the Stroop *Color Word Test* (CWT), more specifically tests the inhibition of prepotent responses. Whether or not inhibition is a core component of the mechanisms of cognitive inflexibility is the subject of some disagreement in the literature; but a failure to inhibit prepotent responses can clearly lead to inflexible behavior. Importantly, responses can become prepotent in a variety of ways; extended repetition during training can increase prepotency, as discussed above in the context of reversal learning, but other responses are prepotent due to extensive prior learning (e.g. the automatic reading of text, in a literate subject) or due to hard-wired reactions (e.g. withdrawal from a noxious stimulus). Whether the ability to inhibit prepotent responses is a unitary capacity or depends on a range of abilities that may be differentially tapped by different tasks is an open question that has not been definitively addressed in studies of OCD.

In the Stroop CWT, subjects view words printed in various colors and are instructed to name the color; the inclination to read the printed word is very strong (i.e. it is prepotent), and thus naming the color when there is a discordance between the word and the color in which it is printed requires effortful inhibition of the prepotent response. The Stroop CWT is similar to some of the set-shifting measures described above in that it requires cognitive inhibition of a prepotent response, but it differs from them in that the prepotent response is innate (or rather overlearned during the acquisition of literacy), not acquired during the task, and in that the instructions do not change during the task. Instructions are provided at the beginning of the task, and contingencies do not change. In these ways, the Stroop CWT may be most similar to TMT-B, though it does not require the motor control and working memory capacities required by the latter measure.

Performance deficits have been described in the Stroop CWT in OCD, with somewhat variable reported effect sizes in the medium range (Stroop-Interference (g=−.55; k=12) (Shin et al., 2013); and [Stroop-Incongruent Time (d=.55; k=16); Stroop Interference: (d=.36; k=18); Stroop Accuracy (d=.39; k=6](Snyder et al., 2015).

In children and adolescents with OCD, white matter integrity in the dorsal cingulum (fractional anisotropy) correlates with better performance in the TMT-B and Stroop (Gruner et al., 2012). The dorsal cingulum bundle is thought to play a critical role in response selection in cognitively demanding information processing tasks; higher FA in this region may reflect a compensation that helps preserve normal behavioral function in the face of competing and conflicting information, especially early in disease course (Gruner et al., 2012).

The *stop signal reaction time task (SRTT) and go/no-go task* are two other commonly used probes that require inhibition of a prepotent response; however, in these cases it is a motor response, not a cognitive one, that must be suppressed. In the SSRT subjects receive a cue instructing them to push a button, but then on a subset of trials they receive a second, subsequent cue instructing them to stop the motor plan that has already been initiated. (The

relative timing of the two cues can be varied to titrate task difficulty and ensure the occurrence of errors.) In the go/no-go task, subjects are instructed to press a button in response to one cue but not to another; the button-press response becomes prepotent because the 'go' cues are presented much more frequently, and thus inhibitory control is required to withhold responding on 'no-go' trials. Whether inhibition of motor responses in these tasks requires the same mechanisms as inhibition of prepotent cognitive responses (as in the Stroop) has been a matter of some debate. Recent work has demonstrated that prefrontal activity associated with inhibition differs during reversal learning and the SSRT (Ghahremani et al., 2010).

Results on these tests of motor inhibitory control have been mixed. Meta-analysis has shown longer reaction times on the SSRT (d=.32; k=17; p=.002); but in the Go/No-go task results are equivocal and not statistically significant, despite the availability of a substantial number of studies (d=.24; k=11; p=.132.) (Snyder et al., 2015). Significantly longer reaction times on the SSRT have been reported in unaffected first degree relatives of OCD probands compared to control subjects (Chamberlain et al., 2007). OCD probands and their siblings have been reported to show greater activity in the left presupplementary motor area during successful inhibition on the SSRT than control subjects; this activation correlates negatively with stop-signal reaction time in probands and siblings (de Wit et al., 2012) and has thus been interpreted as a potential neurocognitive endophenotype. Patients with OCD also show decreased activity in the right inferior parietal cortex and inferior frontal gyrus on this task, relative to both their siblings and controls (de Wit et al., 2012).

Cognitive flexibility in OCD: Updating

Updating is the constant monitoring and rapid addition/deletion of working memory contents (Miyake et al., 2000, Miyake and Friedman, 2012). The ability to successfully update working memory is thought to be a key component of cogntive flexibility (Dajani and Uddin, 2015). The abilty to acquire new information and manipulate it in real time is critical to adjusting one's behavior to meet the demands of a changing enviroment. Updating can be measured through tests such as *the n-back*. In this test, subjects are presented with a continuous sequence of cues (typically letters or numbers) and are instructed to indicate whether the current cue matches the cue presented N trials previously. Difficulty increases in proportion to *n*. Measures such as the *n*-back are typically considered to be probes of working memory and have not traditionally been grouped with measures of cognitive flexibility, but it is increasingly clear that updating is critical to flexible behavior in the face of changing environmental contingencies.

Relatively few studies have explicitly examined updating in OCD. Snyder and colleagues (2015) organized their meta-analysis of EF in OCD around the unity/diversity model (Miyake et al., 2000, Miyake and Friedman, 2012), They found individuals with OCD to exhibit deficits in all three domains of EF, but deficits in updating were of greatest magnitude: (d=.71) (Snyder et al., 2015). The largest impairment was seen on the *n-back* test (Snyder et al., 2015); this task has not been widely used in studies of OCD. More focused research is needed to ascertain whether individuals with OCD have a particular deficit in updating and whether this may contribute to cognitive inflexibility.

Habit, action, and model-based versus model-free learning

Dual-system theories posit that actions and choices may be supported by either a goal-oriented or a habitual system (Balleine and Dickinson, 1998). Recent computational literature draws a similar distinction between model-based and model-free strategies for action selection (Daw et al., 2011). Goal-oriented, model based choice permits flexibility but requires substantial cognitive resources. Habitual or model-free behavior is more efficient in familiar situations, in which past experience provides assurance that a particular course of action is optimal and detailed evaluation of alternatives is therefore no longer necessary. Habitual behavior does not, however, allow for flexibility in the face of a changing environment or changing present and future needs. An over-reliance on habitual behavior may therefore be a source of cognitive and behavioral inflexibility. Importantly, the relationship of habitual behavior to cognitive flexibility, as narrowly defined by some authors (e.g. Dajani and Uddin, 2015), has been little explored; teasing apart the relationship between these constructs is an important goal for future work.

The balance between habitual and goal-directed learning can be probed using devaluation tasks. Typically, a stimulus-outcome association is overtrained; the outcome is then devalued, removing motivation to work for it. Persistent responding despite devaluation is indicative of habit-based (stimulus-response) control of behavior. Recent studies using such paradigms have shown OCD patients to be comparable to controls at learning stimulus/response action patterns that are positively reinforced, but less likely to modify their behavior when particular outcomes have been devalued. Moreover, patients with OCD demonstrated weaker explicit knowledge of the causal relationship between actions and their respective outcome (Gillan et al., 2011). These results suggest an overall reliance on the habit-based as compared to the goal-oriented control system. Using a similar paradigm, but with negative reinforcement, the same group demonstrated that while patients with OCD are comparable to controls at inhibiting unnecessary behavioral responses early in training, they are less able to adjust their behavior when an outcome which previously provided negative reinforcement is devalued and avoidance is no longer necessary (Gillan et al., 2014b).

The constructs of model-based and model-free learning make a similar distinction. *Model-based* denotes learned behavior that requires the construction of an internal representation of task structure to guides choice; this is similar to goal-directed learning (which posits an internal representation of the goal). *Model-free*, on the other hand, describes less flexible but more computationally efficient strategies in which environmental stimuli are directly related to responses, without any need for a mediating internal model of task structure; this is similar to a habit. The balance between model-based and model-free learning has been captured by Daw and colleagues using an innovative behavioral task based on nested probabilistic cue-reward associations (Daw et al., 2011). In a first clinical application of this task, Voon and colleagues found a bias towards model-free learning in individuals with OCD, as well as with bulimia and amphetamine addiction (Voon et al., 2014). This lends further support to the idea that patients exhibit a bias towards less flexible modes of problem-solving.

Abnormalities in goal-directed, model-based control may underlie deficits observed in more traditional neurocognitive tests of cognitive flexibility. Habitual or model-free responses can be considered prepotent, in that the over-learned, habitual response may require effortful suppression for more flexible processes to supercede them (Lee et al, 2014). Many set shifting and reversal learning tasks involve inhibiting a behavior that has become prepotent through repetition and initiating a new response; a bias towards habit learning may underlie enhanced prepotency, and a weakness in more flexible model-based, goal-directed strategies may impede the ability to generate an alternative in the face of a changing environment (Lee et al., 2014).

It is noteworthy that brain regions known to be functionally abnormal in OCD, such as the OFC and the caudate nucleus (Insel, 1992, Maia et al., 2008, Harrison et al., 2009), overlap with those implicated in goal-directed behavioral control (Valentin et al., 2007). Neuroimaging research investigating goal-directed versus habitual control processes in OCD has been limited to date but suggests abnormalities in the mOFC and caudate. Excessive habit formation in an avoidance learning task in OCD has been associated with hyperactivation of the caudate (Gillan et al., 2014a). Patients who did not form excessive avoidance habits were found to hypoactivate the right caudate, compared to healthy volunteers. The OCD group as a whole hyperactivated the medial OFC (mOFC) during the learning of avoidance behaviors. Patients showed decreased mOFC activation over the course of training, whereas controls showed an increase (Gillan et al., 2014a).

Causal reasoning has seldom been explicitly studied in OCD, but it may merit particular attention. Symptoms such as checking are often reinforced by erroneous or even superstitious causal beliefs about the environment. Causal reasoning is by its nature a model-based process and is required for behavioral flexibility in many circumstances. Learning the contingencies between actions and outcomes is necessary for goal-directed behavior, as well as for adaptively adjusting behavior in light of changing environmental contingencies and/or changing outcome values. When actions are highly causal, activity in medial OFC and caudate increases (Tanaka et al., 2008). As noted above, after learning a stimulus-response task, individuals with OCD have been found to have a poorer understanding of the causal relationships within the task (Gillan et al., 2011). Over-reliance on habit in OCD may be the result of impaired or abnormal causal learning. Such impairments may lead to behavioral inflexibility in the face of changing goal value.

Adaptive behavior requires on-line *arbitration* between goal-oriented and habit-like systems as environmental contingencies change. A recent study implicated a region of the rostral anterior cingulate cortex (rACC), which is also hyperactive in OCD, in computing the differential predictive reliability of the goal-oriented and habitual control systems (Lee et al., 2014). Computing this difference is critical for arbitrating between the two systems in real time (Lee et al., 2014). In OCD, aberrant regulatory processes, such as arbitration between competing action strategies (Gruner et al., 2015), may lead to inflexibility by impairing the ability to dynamically switch between alternative behavioral strategies in an inconsistent environment.

The paradox of broad executive function deficits in OCD

The specificity of the findings summarized above has been questioned. In particular, three meta-analyses of cognitive function in OCD describe deficits of moderate effect size across almost all domains of executive function, including planning, verbal fluency, visuospatial function, and motor speed (Abramovitch et al., 2013, Shin et al., 2013, Snyder et al., 2015). (Verbal working memory may be relatively spared; Snyder et al., 2015). This raises the question of whether deficits in cognitive inflexibility are particularly characteristic of patients with OCD and are important to its pathophysiology, as we have suggested, or whether they are just an instance of a broader, nonspecific cognitive impairment.

The finding of broad deficits across multiple cognitive domains in OCD is incongruous, as most patients are not obviously cognitively impaired in many aspects of their lives. Broad executive function impairments are also seen in schizophrenia, in which real-world cognitive difficulties are pervasive (e.g. Fatouros-Bergman et al., 2014). But OCD is not thought to simply be a *forme fruste* of schizophrenia; clinically, the difficulties patients have in cognitively demanding situations are quite distinct in the two disorders, at least in typical cases. The presence of deficits across multiple domains therefore represents a conundrum, and a challenge to the idea that deficits in cognitive flexibility are specifically relevant to clinical symptoms.

Standard tests of cognitive flexibility, and of executive function more generally, do not map unambiguously onto unitary underlying constructs. This is emphasized by Table 1, which illustrates that all of the tasks we have reviewed map onto multiple constructs. With the added observation that the constructs listed may not be unitary natural kinds – that is, they may not prove to correspond in a simple way to the underlying organization of information processing and behavioral control in the brain – an inevitable conclusion is that most or all of our standard neuropsychological assessments are not sufficiently specific to allow us to identify discrete areas of deficit in particular neuropsychiatric conditions. Deficits across a range of domains, such as are seen in both OCD and schizophrenia, may therefore be a sensitive indicator of psychopathology in general, but a poor marker for specific disease processes. More specific behavioral probes, based on an evolving understanding of the underlying brain processes that support different domains of executive function, are required.

Individuals with severe OCD are preoccupied with obsessional thoughts most or all of the time and often feel a need to devote cognitive resources to responding to or attempting to control them; it is easy to imagine that these could interfere with performance in a wide range of tasks, irrespective of the specific task demands – as if they were always attempting to perform demanding cognitive tasks in a noisy room. This has been framed as the ‘executive overload’ hypothesis of deficit in OCD (Abramovitch et al., 2012). Under this interpretation, deficits across a range of domains of executive function may be real but epiphenomenal.

A third possible explanation for the range of executive function deficits seen in OCD is that OCD is not a unitary disorder, and that different component conditions (or continua) are

characterized by distinct deficits, such that the broad deficits described in meta-analysis are reasonable descriptions of a heterogeneous population but are not accurate characterizations of individual patients. Clinically, OCD is particularly heterogeneous, and substantial research effort has been devoted to characterizing underlying dimensions or subtypes (e.g. Bloch et al., 2008). Characterizing particular constellations of deficits that may correlate with particular symptomatic presentations will require systematic characterization of multiple domains of function and detailed clinical assessments in large numbers of patients. This is a daunting undertaking but may represent an important step towards the goal of personalized medicine targeting individual patients' deficits, rather than generic and heterogeneous syndromes.

Given the observation that individuals with OCD have deficits across multiple domains of executive function, what justification is there for a particular focus on cognitive inflexibility? The first is face validity: cognitive inflexibility maps well onto core OCD symptomatology, particularly patients' tendency to get 'stuck' in patterns of thought or behavior and their extreme difficulty switching away from them. A second justification is evidence for inflexibility in recent studies using modern, theory-grounded probes of habit-like learning, which contain internal behavioral controls and may be more specific than classical neuropsychological tests (Gillan et al., 2011, Gillan et al., 2014b, Voon et al., 2014). A third is the documentation of inflexibility in first degree relatives of individuals with OCD, which suggests that such deficits may represent endophenotypes of the disorder and thus, plausibly, be closer to core pathophysiology (Chamberlain et al., 2007, Chamberlain et al., 2008). A fourth is the identification of altered brain activity in OCD brain regions clearly associated with cognitive flexibility, such as the OFC, caudate, and putamen, and the impaired recruitment of these regions in a range of behavioral tasks requiring cognitive inflexibility, as summarized at length above.

Nevertheless, it is clear that further careful work is require to precisely characterize specific cognitive deficit(s) that may contribute to symptomatology and the phenomenology of cognitive and behavioral inflexibility in patients with OCD. Both the measurement of unitary constructs using behavioral probes and the distinction between core deficits and epiphenomena represent profound experimental challenges. The ongoing integration of brain imaging with increasingly precise behavioral assessments is likely to add critical insight in this project.

Sources of impaired performance in tests of cognitive flexibility

Implicit in the above discussion is the realization that there are multiple possible sources of impaired performance in behavioral tasks that purport to measure cognitive flexibility. Careful consideration of these different sources of variation, and exclusion of them when possible, will facilitate more precise characterization of the nature of cognitive abnormalities in patients.

1. First, there may be a true group difference in the cognitive ability that a behavioral task is seeking to probe. This is the conclusion that one wishes to support (or exclude) in most instances.

2. Second, there may be deficits in other cognitive or procedural capacities that influence performance on the task being investigated. This is the same as saying that a behavioral task may not be a specific probe of the specific cognitive capacity that it is seeking to assay; as is emphasized above and in Table 1, this is the case for most or all standard neurocognitive assessments. Enhanced confidence that one is measuring the construct of interest can come from careful design of behavioral tasks, and from the use of multiple behavioral probes in an effort to converge on a shared construct.

3. Third, there may be compensatory processes at play. There is good evidence that this is the case in OCD, at least in some tasks (Deckersbach et al., 2002, de Wit et al., 2012, Gruner et al., 2012, Remijnse et al., 2013). Compensatory processes may enable normal or only subtly perturbed performance despite substantial abnormalities in underlying capacities. Brain imaging studies are likely to be essential for identification of such compensatory processes in the face of preserved task performance; altered patterns of brain activity during task performance in patients, relative to controls, suggest that key brain circuitry is being differentially recruited. An additional strategy to reveal the presence of compensated deficits is to manipulate task requirements so as to interfere with compensatory processes; in a few cases, this approach has been used to unmask deficits in OCD that were not otherwise apparent (Deckersbach et al., 2002). Of course, the interpretation of deficits that emerge only in the presence of imposed cognitive load will be more complicated than those that emerge in simpler tasks.

4. Fourth, performance may be compromised by various sources of distracting ‘noise’ that interfere with task performance. This may be due to enhanced sensitivity to external distractors, which is often seen in OCD, or to enhanced ‘internal noise’, such as distracting intrusive cognitions (e.g. obsessions). Such increased noise may be a source of deficits across a wide range of cognitive tasks.

5. Finally, baseline or fluctuating alterations in motivation may also nonspecifically affect performance. Motivation can obviously be impaired in many psychiatric disorders; in OCD, it can also be enhanced, due for example to characterological perfectionism exhibited by many patients. Well-designed behavioral tasks can use well-matched control conditions to control for motivational factors; however, this is rarely done in classical neuropsychological measurement.

Different combinations of these sources of variance may combine to give very similar patterns of behavioral impairment (or lack thereof) in individual tasks. Multiple sources of information will need to be integrated to clarify underlying pathology: convergent evidence from well-defined and internally controlled behavioral probes of clearly operationalized underlying constructs; neuroimaging to delineate the neural circuitry associated with particular tasks and constructs, and how it differs between diagnostic groups; studies in first-degree relatives that may identify behavioral and neural endophenotypes, independent of frank clinical symptomatology.

Conclusions

Obsessive-Compulsive Disorder (OCD) is characterized by maladaptive patterns of repetitive, inflexible cognition and behavior that suggest a lack of cognitive flexibility. In keeping with this, many neurocognitive studies of individuals with OCD suggest behavioral and/or neurobiological abnormalities in cognitive flexibility (Remijnse et al., 2006, Chamberlain et al., 2007, Chamberlain et al., 2008, Gu et al., 2008, Viswanath et al., 2009). Meta-analytic reviews of neuropsychological functioning in OCD, as well as clinical observations, support a pattern of cognitive inflexibility in OCD. We have attempted to summarize this complex literature, while also highlighting areas of uncertainty and conceptual challenges to the field.

OCD is associated with impairments in measures of attentional set shifting, alternation, reversal learning, cognitive control measures such as TMT-B and the Stroop CWT, and motor inhibition as measured by the stop signal task; all of these deficits appear to be of moderate effect size, at least in meta-analysis. Behavioral or neurobiological differences in alternation, attentional set shifting, and motor inhibition have also been observed in first-degree relatives, suggesting that these abnormalities may be endophenotypes for OCD. Underactivation of prefrontal regions, especially the OFC, during task performance has been demonstrated in OCD with particular regularity (Remijnse et al., 2006, Chamberlain et al., 2008, Gu et al., 2008, Remijnse et al., 2013).

However, as emphasized throughout our discussion, much remains unclear. One question is whether cognitive inflexibility is a distinct pathology or is merely a reflection of some broader deficit in executive function. A second is whether this deficit is specific to individuals with OCD, or rather (since it is surely not specific to OCD as currently defined) what characterizes the range of clinical conditions in which cognitive inflexibility is prominent, and what other characteristics interact with difficulties with cognitive flexibility to produce the distinguishing symptoms among these diagnoses. A third question is whether and how cognitive inflexibility contributes to clinical symptomatology – it is intuitive for any clinician who has worked extensively with individuals with OCD that there is likely to be a relationship, but there is as yet no clear explanatory framework within which to formalize and test this intuition.

Ultimately, it is likely that classical neuropsychological tests will not be adequate to resolve these questions. A new generation of behavioral tasks grounded in clearly enunciated hypotheses about the underlying organization of executive function in the brain, bolstered by the use of functional neuroimaging to characterize cases in which different patterns of neural organization and recruitment can lead to similar behavioral performance, will be necessary to clarify how cognitive flexibility is disrupted in OCD.

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Highlights

- Deficits in cognitive flexibility have been described in obsessive compulsive disorder (OCD).
- These deficits may contribute to symptomatology.
- Classical neuropsychological probes test multiple constructs simultaneously.
- More specific behavioral tests, supplemented by neuroimaging, are needed.

Task	Description	Construct(s) probed	Findings in OCD	References
Object Alternation Task (OAT)	Subjects select from among 2 or more objects; the same object is never rewarded twice in a row, and so optimal performance requires shifting objects on every trial	Contingency learning Affective set shifting Working memory for objects	Results from OAT & DAT combined in meta-analyses. > perseverative errors in OCD compared to controls (g=−.48; k=5). Decreased accuracy scores by OCD compared to controls (d=.32; k=17). Unaffected siblings of OCD probands also shown to demonstrate deficits on the OAT.	Shin et al., 2013 Snyder et al., 2015 Viswanath et al., 2009
Delayed Alternation Task (DAT)	Subjects select a location in space on each trial; the rewarded location alternates, such that optimal performance requires shifting to a new location in space on every trial	Contingency learning Affective set shifting Spatial working memory	Results from OAT & DAT combined in meta-analyses. > perseverative errors in OCD compared to controls (g=−.48; k=5). Decreased accuracy scores by OCD compared to controls (d=.32; k=17).	Shin et al., 2013 Snyder et al., 2015
Reversal learning	A particular cue is rewarded (consistently or intermittently); at some point, unsignaled to the subject, reward contingencies switch, such that previously rewarded cues are no longer rewarded (or are rewarded less), and previously neutral cues are now rewarded (or are rewarded more)	Contingency Learning Affective set shifting Inhibition of prepotent response Working memory	Tasks tend to be non- standardized; more difficult to meta-analyze. Neuroimaging has revealed differences in brain activation, despite normal performance on reversals, with the patient group underactivating prefrontal regions including the OFC. Decreased responsiveness in the right caudate has also been noted in pts on rewarded trials. Decreased prefrontal activation has been noted in unaffected healthy relatives of probands. Subtle behavioral differences on tasks.	Chamberlain et al., 2008 Remijnse et al., 2006 Valerius et al., 2008
Wisconsin Card Sort Task (WCST)	Complex cards must be sorted on the basis of one characteristic (e.g. color, number, shape); unsignaled to the subject, the salient characteristic shifts after 10 correct responses, and subjects must learn the new rule through trial and error	Contingency learning Attentional set shifting Extradimensional set shifting Intradimensional set shifting Working memory	Increased perseverative errors on the WCST indicated by two meta-analyses (g=−.51; k=21) and (d=.44; k=42). Significantly larger effects reported with computerized version than with the classic manual version	Shin et al., 2013 Snyder et al., 2015
Intradimensional /Extradimensional Shift Task (IED) from the Cambridge Neuropsychological Test Automated Battery (CANTAB)	One of two cards containing simple or compound stimuli (consisting of one or two dimensions: color filled shapes and white lines) must be selected. Feedback teaches the subject which stimulus is correct; and after six correct responses, the stimuli and/or rules change. Subjects must learn rules through trial and error.	Contingency learning Attentional set shifting Extradimensional set shifting Intradimensional set shifting Affective set shifting/ reversals Working memory	Significant deficit for ID shifting [g= .37; k=5, p=.004)], with a weaker and non-significant effect on ED shifting [g=−.31; k=6, p=.068). Significant deficit in the overall accuracy of shifting in the IED (d=.50; k=7, p=<.001). Deficits identified in unaffected first-degree relatives of probands with OCD.	Shin et al.,2013 Snyder et al., 2015 Chamberlain et al., 2007
Task switching	Subjects choose among stimuli based	Attentional set shifting Task switching	One meta-analytic review has demonstrated abnormality at trend	Snyder et al., 2015

Task	Description	Construct(s) probed	Findings in OCD	References
	on one of several dimensions (e.g. color, number, shape); a change in which stimulus characteristic is to be attended to is explicitly signaled by a cue.	Inhibition of prepotent response Working memory	level with a medium effect size (d=.35; k=3; p=.089). One study found performance of OCD patients more accurate but slower than controls; accuracy increased linearly with the severity of symptoms. Consistent neuroimaging finding of reduced activation of prefrontal regions including OFC and DLPFC in OCD. One study found increased activation of the left putamen, bilateral anterior cingulate cortex (ACC), and left postcentral gyrus in OCD. Abnormalities may be state dependent.	Remijnse et al., 2013 Gu et al., 2008 Vriend et al., 2013
Trail Making Task (TMT) – PartB	Subjects draw a line alternating between consecutive letters and numbers (A-1-B-2-C-3….)	Attentional set shifting Task switching Updating working memory Inhibition of prepotent response	Deficit demonstrated with consistent effect sizes across recent meta-analytic reviews: (g=−.49; k=22) and (d=.54; k=37) In children and adolescents, one study showed a correlation between higher FA in the cingulum bundle and greater performance on the TMT-B and Stroop CWT.	Shin et al., 2013 Snyder et al., 2015 Gruner et al., 2012
Stroop color-word test (CWT)	Subjects are presented with the names of colors, printed in either the same or a different color; they are instructed to name the color in which the text is printed, producing conflict when this differs from the text.	Cognitive inhibition of a prepotent response	Performance deficits in OCD, with somewhat variable effect sizes in the medium range (Stroop-Interference (g=−.55; k=12); and [Stroop-Incongruent Time (d=.55; k=16); Stroop Interference: (d=.36; k=18); Stroop Accuracy (d=.39; k=6]. In children and adolescents, one study showed a correlation between higher FA in the cingulum bundle and greater performance on the TMT-B and Stroop CWT.	Shin et al.,2013 Snyder et al., 2015 Gruner et al., 2012
Stop signal reaction task (SSRT)	Subjects are given a cue instructing them to press a button; then on a subset of trials they are given a second cue instructing them to withhold the (already-initiated) response.	Motor inhibition of a prepotent response	Meta-analysis has shown longer reaction times in OCD (d=.32; k=17; p=002). Significantly longer reaction times also shown in unaffected first degree relatives of OCD probands compared to controls. OCD probands and their siblings show greater activity in the left presupplementary motor area during successful inhibition than controls. Patients with OCD show decreased activity in the right inferior parietal cortex and inferior frontal gyrus on this task, relative to both their siblings and controls.	Snyder et al., 2015 Chamberlain et al., 2007 de Wit et al., 2012
Go/no-go task	Subjects are presented with a series of cues; they are instructed to press a button in response to one (typically the more common) but to withhold the button-press in response to	Motor inhibition of a prepotent response	Meta-analysis has not shown a significant difference in performance compared to controls, across a substantial number of studies (d=.24; k=11; p=.132).	Snyder et al., 2015

Task	Description	Construct(s) probed	Findings in OCD	References
	another.			
N-back task	Subjects are presented with a continuous sequence of cues (typically letters or numbers) and are instructed to indicate whether the current cue matches the cue presented N trials previously. Difficulty increases in proportion to N.	Working memory Updating	Meta-analysis has shown a significant difference in performance with a large effect size (d=.71; k=4; p=.002).	Snyder et al., 2015