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Arbitration between action strategies in obsessive-compulsive disorder

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Abstract

Decision-making in a complex world, characterized both by predictable regularities and by frequent departures from the norm, requires dynamic switching between rapid habit-like, automatic processes and slower, more flexible evaluative processes. These strategies, formalized as ‘model-free’ and ‘model-based’ reinforcement learning algorithms, respectively, can lead to divergent behavioral outcomes, requiring a mechanism to arbitrate between them in a context-appropriate manner. Recent data suggest that individuals with obsessive-compulsive disorder (OCD) rely excessively on inflexible habit-like decision-making during reward-driven learning. We propose that inflexible reliance on habit in OCD may reflect a functional weakness in the mechanism for context-appropriate dynamic arbitration between model-free and model-based decision-making. Support for this hypothesis derives from emerging functional imaging findings. A deficit in arbitration in OCD may help to reconcile evidence for excessive reliance on habit in rewarded learning tasks with an older literature suggesting inappropriate recruitment of circuitry associated with model-based decision-making in unreinforced procedural learning. The hypothesized deficit and corresponding circuitry may be a particularly fruitful target for interventions, including cognitive remediation.

Introduction and hypothesis

Obsessive-compulsive disorder (OCD) is a frequently disabling condition that affects 1.3% of the population in any given year and 2.7% at some point during their lives (Kessler and others 2012; Ruscio and others 2010). It negatively affects patients’ social and vocational functioning, sense of emotional and physical well being, and global quality of life, producing substantial morbidity (Koran 2000). OCD is associated with subtle cognitive

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deficits. It has been speculated that these deficits are associated with functional impairment and may contribute to symptoms (Fineberg and others 2010). In particular, many studies suggest problems with cognitive flexibility (Chamberlain and others 2007; Chamberlain and others 2008; Gu and others 2008; Remijnse and others 2006; Viswanath and others 2009). For example, traditional neuropsychological studies of OCD indicate neurocognitive deficits in attentional/ extra-dimensional set shifting (Chamberlain and others 2007), affective set shifting/reversal learning (Chamberlain and others 2008; Remijnse and others 2006), and task shifting (Gu and others 2008). Behavioral abnormalities and dysfunction of associated neural systems have also been demonstrated in unaffected first degree relatives of probands with OCD on measures of set shifting (Chamberlain and others 2007; Chamberlain and others 2008; Viswanath and others 2009), suggesting that cognitive inflexibility may be an endophenotype for the disorder.

Meta-analyses of tests of neuropsychological functioning in adults with OCD have demonstrated impairments in set shifting/cognitive flexibility and overall executive function, with medium mean effect sizes (Abramovitch and others 2013; Shin and others 2013). There is substantial heterogeneity in these assessments – for example, significantly larger effect sizes are detected for attentional set shifting deficits in OCD when using a computerized version of the Wisconsin Card Sorting Test (WCST) than when using the classic manual version (Shin and others 2013) – and different constituent processes may contribute to the categorical deficits identified in these meta-analyses. Nevertheless, this literature broadly supports the overall pattern of cognitive inflexibility in OCD.

Taken together, these results suggest that individuals with OCD have difficulty inhibiting an established response in the face of new contingencies, whether switching attention from one dimension of a stimulus to another (Chamberlain and others 2007) or suppressing or reversing a previously rewarded response (Chamberlain and others 2008; Remijnse and others 2006). This pattern of inflexibility seems to occur both in situations in which learning is required to establish a new behavioral pattern (Chamberlain and others 2007; Chamberlain and others 2008; Remijnse and others 2006) and when patients are directed to follow a new instruction (Gu and others 2008). Furthermore, it is present in situations involving reinforcement, punishment (Chamberlain and others 2007; Chamberlain and others 2008; Remijnse and others 2006), or no feedback at all (Gu and others 2008).

This pattern of cognitive inflexibility in OCD has been interpreted using dual learning systems theory (Balleine and Dickinson 1998; DawNiv and Dayan 2005; Lee, Duman and Pittenger 2008; Poldrack and others 2001). According to this framework, actions and choices may be supported by either a goal-oriented or a habitual mechanism (Balleine and Dickinson 1998). Recent computational literature draws a similar distinction between model-based and model-free strategies for action selection (Daw and others 2011; Daw and others 2005). Goal-oriented, model-based choice explicitly takes into account a desired outcome and permits flexibility, but it is slow and requires substantial computational resources (Daw and others, 2005). Habitual or model-free behavior is more efficient in familiar situations, in which past experience provides assurance that a particular course of action is appropriate and detailed evaluation of alternatives is superfluous (Daw and others, 2005). Habitual behavior does not, however, allow for flexibility in the face of a changing

environment or changing present and future needs. Some individuals or populations may rely disproportionately on one system or the other (Voon and others 2014). Optimal performance in a complex world requires the use of both systems and the capacity to dynamically switch between them.

Animal studies have associated goal-directed action with activation of the medial prefrontal cortex and dorsomedial striatum (DMS), whereas habits have been associated with the sensory-motor cortices and dorsolateral striatum (DLS) (Dezfouli and Balleine 2012). Functional magnetic resonance imaging (fMRI) studies in humans have indicated a similar dissociation. Activity in the orbital frontal cortex (OFC) is associated with goal-directed choice (Valentin and others 2007), and both the OFC and the caudate nucleus are involved in encoding the causal effects of actions (Tanaka and others 2008), an important aspect of goal-directed behavior. Goal-directed and habitual behavior can be at least partially competitive at the level of the striatum (Dezfouli and Balleine 2012; LeeDuman and Pittenger 2008; Yin and others 2005, 2006). Specifically, blocking activity in the DMS through lesions or pharmacological manipulations causes goal-directed behavior to become habitual, whereas blocking activity in the DLS renders habitual behavior goal-directed (Dezfouli and Balleine 2012; Quinn and others 2013; Yin and others 2005, 2006).

In this framework, cognitive inflexibility in OCD might result from a deficiency in mechanisms underlying goal-oriented processes or an over-reliance on mechanisms subserving habitual processes (Gillan and Robbins, 2014). It remains unclear, however, which, if either, of these abnormalities is the primary problem driving behavioral abnormalities. Given the evidence for a competitive balance between the systems, it seems plausible that weaknesses in goal-oriented control may lead to an overreliance on the habitual control system over time; however, it seems equally possible that an initial proclivity to over-rely on habitual control might lead to atrophy of the goal-oriented control system over time.

We propose a third possibility: that a primary problem in OCD lies not in the internal dynamics of the goal-oriented or habit system, but in an inability to dynamically and flexibly switch between them in a context-appropriate manner (Figure 1). As we discuss below, this hypothesis may help us to explain data in the literature that are otherwise difficult to reconcile. More precisely identifying the core neurocognitive deficit underlying dysfunction across a variety of experimental paradigms may facilitate the design of cognitive treatments specifically tailored to remediate the underlying difficulty.

Goal-directed and habitual control of action in OCD

It has been suggested that cognitive inflexibility and an over-reliance on habit-like behavioral control may underlie compulsions (Gillan and Robbins, 2014). This is plausible whether this increased reliance derives from abnormalities in the habit (model-free) system, the more flexible model-based system, or the capacity to mediate between them. Abnormal habit-like or model-free behavioral control has been associated with abnormalities of the cortico-striatal system (Yin and others, 2006; Graybiel, 2008), and direct manipulation of corticostriatal projections has recently been shown to modulate compulsive grooming, which

may model aspects of the phenomenology of OCD, in animals (Ahmari and others, 2013; Burguière and others, 2013).

Individuals with OCD have disrupted goal-directed action control in a positively-reinforced instrumental paradigm (Gillan and others 2011). While patients are comparable to controls at learning stimulus-response-outcome relationships under positive reinforcement, they are less likely to modify their behavior when specific outcomes have been devalued – that is, they rely on a stimulus-driven habit, independent of outcome. Moreover, despite being comparable to controls at using external positive feedback to guide instrumental choice during learning, patients with OCD demonstrate weaker explicit knowledge of the causal relationship between actions and outcomes. In a similar paradigm using negative reinforcement, while patients with OCD are comparable to controls at inhibiting unnecessary behavioral responses early in training, they show greater avoidance habits than controls following overtraining (Gillan and others 2014). Specifically, OCD patients are less likely to adjust their behavior when negative reinforcement is devalued and avoidance is no longer necessary.

Other paradigms have been used to probe implicit learned behaviors in OCD. While the work of Gillan and others (2011, 2014) suggests over-reliance on habit and weak goal-directed control in OCD, earlier studies of procedural learning in OCD show, in contrast, an anomalous recruitment of goal-directed systems during implicit learning tasks that are generally striatum-dependent in healthy individuals (Deckersbach and others 2002; Joel and others 2005; Rauch and others 1997; Rauch and others 2007). In a serial reaction time (SRT) task, for example, patients with OCD show aberrant recruitment of medial temporal lobe and orbitofrontal circuits more typically associated with explicit or goal-directed learning, yet they perform the task adequately (Rauch and others 1997; Rauch and others 2007). This suggests inappropriate recruitment of the goal-directed system, even though it may be less well suited to the task. When this circuitry is otherwise recruited by simultaneous performance of an explicit memory task, a subtle behavioral deficit emerges in OCD patients (Deckersbach and others 2002). Similarly, in an implicit learning task in which explicit processing actually impairs acquisition, OCD patients are impaired, compared to both controls and patients with major depressive disorder (Joel and others 2005).

Thus, findings in a variety of implicit learning paradigms (Deckersbach and others 2002; Joel and others 2005; Rauch and others 1997; Rauch and others 2007) contrast with the findings of Gillan and others in instrumental habit learning (Gillan and others 2014; Gillan and others 2011; Voon and others 2014): the former indicate an over-reliance on the explicit, goal-directed system, whereas the latter suggest weaknesses in the goal-directed system and an over-reliance on habit. One possible explanation for this discrepancy is that the two categories of task are tapping into fundamentally distinct underlying constructs. However, implicit learning tasks such as the SRT have much in common with habit learning. Both implicit learning and habit learning tasks entail behavior that becomes increasingly automatic and stereotyped with practice, as subjects eschew detailed evaluation of alternatives. Both become so routine that subjects carry them out without conscious effort (hence, ‘implicit’). Thus, both stand in contrast to goal-oriented control, which is generally an explicit process accompanied by awareness of the decisions being contemplated and

executed. Finally, both recruit the cortico-basal ganglia circuitry, particularly the sensorimotor cortex and the dorsal striatum (especially the dorsolateral striatum/putamen).

If these two categories of task do tap fundamentally similar underlying capacities, then the idea that habit-like learning is enhanced in OCD, or that goal-directed learning is fundamentally deficient, does not suffice to explain the observed results. Some other explanation is needed.

Arbitration between model-free and model-based systems

To reiterate: some studies indicate an over-reliance on the explicit, goal-directed system (Deckersbach and others 2002; Joel and others 2005; Rauch and others 1997; Rauch and others 2007) in OCD, while other research suggest weaknesses in the goal-directed system and an over-reliance on habit (Gillan and others 2014; Gillan and others 2011; Voon and others 2014). If these implicit learning tasks and habit learning are in fact tapping the same or similar capacities and mechanisms (we will use the term ‘model-free’ to encompass both), then we must conclude that model-free learning dominates over model-based strategies only in some contexts, not in general.

Considering learning systems in isolation may be too simplistic. The effects of brain pathology on learning or decision-making can depend critically on interactions between learning systems. For example, in a navigational learning paradigm in mice, disruption of the dorsal striatum both impairs striatum-dependent cue-driven learning and accelerates hippocampus-dependent spatial learning; this has been interpreted as evidence of competition between goal-directed and habit-based systems (Lee and others 2008). Similar evidence for competition between striatum-dependent and DLPFC-dependent learning has been shown in fMRI studies in humans (Doll and others 2014; Poldrack and others 2001; Simon and Daw 2011).

These observations highlight the brain’s capacity to arbitrate, in real time, between model-free and model-based decision-making (Figure 1). We speculate that dysfunction in this ability to select and utilize the optimal mechanism for the task at hand, and in the ability to dynamically and flexibly switch control as circumstances require, may account for many of the behavioral problems with cognitive flexibility that are seen in OCD. A neural system that is associated with such real-time arbitration would thus be a candidate locus of pathology and a potential target for therapy.

Lee and others (2014) recently identified neural substrates associated with the arbitration between goal-directed and habitual control during reinforced learning. They used functional magnetic resonance imaging (fMRI) during a sequential decision-making task, in which outcomes are partly under the control of the subject but also partly random. They tested and validated a hybrid computational model consisting of goal directed (or model-based) and habitual (or model-free) learning processes, and characterized the neural substrates underlying these processes. Their decision-making task included both specific-goal trials that encourage a more goal-directed strategy and flexible-goal trials that encourage habitual

control, as well as both high and low levels of uncertainty in state-action-state transition probabilities, which should elicit habitual and goal-directed control, respectively.

Their analysis implicated three frontal regions in arbitration under reinforcement. Activity in anterior regions of the inferior lateral prefrontal cortex (ilPFC) bilaterally (MNI coordinates of peak voxels: -54, +38, +3 and +48, +35, -2) correlated with both model-based and model-free reliability signals. Activity in these two regions and in an additional region of the right frontopolar cortex (FPC) (MNI coordinate of peak voxel: +15, +56, +25) correlated best with whichever system had the maximum reliability, or made the better predictions, on a trial-by-trial basis. Additionally, activity in a region of the anterior cingulate cortex (ACC) (MNI coordinate of peak voxel: +3, +32, +10) correlated with the difference in reliability between the goal-oriented and habitual control systems, suggesting that this part of the ACC may be involved in comparing the predictive values of the two systems (Lee and others 2014).

Next, in a psychophysiological interaction (PPI) analysis, Lee and others found that model choice probability (the extent to which the goal-directed/model-based system controls behavior) modulates the effective connectivity of these arbitrator regions with regions associated with the habitual control of behavior. Specifically, when the modeled 'arbitrator' favored the goal-directed system, there was a significant negative coupling between the arbitrator regions (ilPFC and FPC) and the putamen, one of the main regions activated by the habitual control or system. Somewhat unexpectedly, no such relationship was found between the arbitrator regions and the neural substrates of the goal-directed system. This suggests that, in this reinforced task, the arbitrator predominantly works by gating the habitual control (model-free) system, which may be the brain's default strategy. Goal-directed decision making under these circumstances may require arbitrator regions to actively inhibit habitual control (Lee and others 2014).

These studies are broadly consistent with findings in rodents, although mapping between subregions of the prefrontal cortex in rodents and humans is imprecise. In mice and rats, extended operant training can render a behavior habitual; this depends on the function of the dorsolateral striatum, roughly analogous to the primate putamen (Yin and others 2005, 2006; Quinn and others 2013). Modulation of this circuitry by the infralimbic cortex leads animals to switch between goal-directed and habit-like behavioral modes (Hitchcott and others 2007; Smith and Graybiel 2013), suggesting that this prefrontal region may serve as a substrate for arbitration between the two systems.

Abnormal arbitration in OCD?

We suggest that in individuals with OCD performing reinforced learning tasks, a deficient arbitration system leads to an impaired ability to dynamically modulate the habit-driven system, which is a default computational process, at least in reinforced tasks. Comparison of neural abnormalities in OCD with those associated with the function of the arbitrator system (Lee and others 2014) supports this possibility, as further elaborated below. This hypothesis is consistent with observations that OCD patients appear to be both deficient in goal-

oriented control and over-reliant on habitual processes in a reinforced stimulus-response task (Gillan and others 2011; 2014).

Such a deficit could in theory explain both over-reliance on habit-like learning in some tasks and over-reliance on goal-directed processes in others. In the absence of a fully functional arbitrator, subjects may be ‘stuck’ in the model-free mode in reinforced tasks such as those explored by Gillan and others (2011, 2014) and by Lee and others (2014), unable to efficiently switch to a model-based decision-making strategy even when it would be better suited to the task at hand. Over time, over-reliance on circuitry subserving model-free decision making and impaired recruitment of circuitry involved in model-based processing might lead to plastic changes in both systems.

Aberrant recruitment of medial temporal lobe structures normally associated with model-based learning during the implicit SRT task may represent a different type of inefficient arbitration between parallel systems. The habit learning tasks (Gillan and others 2011, 2014; Voon and others 2014) and the task used by Lee and others to characterize the arbitrator are reinforced on a trial-by-trial basis. The SRT task (Deckersbach and others 2002; Rauch and others 1997, 2007) is fundamentally different, in that it is not explicitly reinforced. More theoretical and experimental work is needed to clarify dynamic interactions between model-free and model-based systems in the absence of differential reinforcement. Irrespective of these details, an inability to dynamically and flexibly switch between systems in a context-appropriate manner in OCD is seen across these distinct literatures.

Recent neuroimaging analyses are consistent with a dysfunction of the substrates of the arbitration system in individuals with OCD. We used a data-driven global brain connectivity (GBC) analysis of resting-state fMRI data to identify areas of abnormal functional connectivity in the brains of individuals with OCD (Anticevic and others 2014). Such GBC analyses do not require the *a priori* specification of a seed against which to compute functional connectivity and thus provide an unbiased examination of brain functional architecture. This analysis identified a cluster of voxels within the anterior portion of left ilPFC, overlapping with the region identified by Lee and others (see Figure 2), in which GBC is reduced in OCD patients relative to matched healthy controls. This region (MNI coordinate of peak voxel: -49, +44, -9; cluster size: 2187mm³) was identified independently in both a whole-brain GBC analysis and a prefrontal cortex (PFC)-restricted analysis, adding convergent evidence for this effect.

A more traditional seed-based functional connectivity study in OCD patients (Harrison and others 2009) also found abnormalities in this region. These authors computed voxelwise statistical parametric maps of functional connectivity with 4 striatal regions of interest, defined *a priori*. The dorsal putamen had reduced functional connectivity with bilateral ilPFC in patients with OCD compared to controls (MNI coordinates of peak voxels in OCD pts: -38, +24, +10 and +49, +28, +1). The putamen, one of the main regions activated by the habitual control or model free system, is a particularly relevant seed in the current context, as it was identified as being regulated by the arbitrator regions (Lee and others 2014).

Taken together, these results suggest reduced functional connectivity in the anterior ilPFC in OCD, with related dysfunction of the ability of this region to regulate habit-related circuitry centered in the putamen. While the ilPFC has not been a major focus of study in OCD, it does exhibit reduced grey matter volume in medication-free OCD patients compared to healthy controls in an MRI study using whole-brain voxel-based morphometry (VBM) (MNI coordinate of peak voxel: -50, +20, +16; cluster size: 132 voxels) (van den Heuvel and others 2009).

In order to better understand the functional architecture of anterior ilPFC, we computed brain-wide voxel-wise functional connectivity with the region in the anterior portion of left ilPFC in which we found GBC reduced in OCD patients relative to matched healthy controls (Anticevic and others 2014), and which Lee and others found to be associated with arbitration. Figure 3A shows the results of this functional connectivity analysis in 96 healthy control subjects. We compared our data to the 7 network parcellation of the cerebral cortex conducted by Yeo and others (2011) (see Figure 3B). As is qualitatively depicted in the figures, components of the cluster within ilPFC appear to be part of both the frontoparietal control and default-mode networks. The left ilPFC area seems to be functionally coupled with aspects of both systems (see Figure 3A). The frontoparietal control system is hypothesized to support cognitive control and decision making processes such as simultaneous consideration of multiple interdependent contingencies (Vincent and others 2008), and may also be involved in adjudicating between potentially competing inner (default-mode network) versus outer directed processes (Vincent and others 2008).

As noted above, a region of the right frontopolar cortex (FPC) also correlated with the arbitration signal in the study of Lee and others. This region is slightly superior to Brodmann area (BA) 10 (within BA 9) and closest to what has been described as lateral frontal pole (FPI) in parcellation studies of the FPC (Liu and others 2013). This region is closely associated with the immediate adjacent parts of the dorsolateral prefrontal cortex (DLPFC) and is implicated in performance of executive processing tasks under high cognitive load (Liu and others 2013). While a role for this particular cluster within FPC in OCD pathology is presently unknown, nearby regions within BA 10 have decreased grey matter volume in OCD patients compared to controls (van den Heuvel and others 2009), decreased GBC (Anticevic and others 2014), and decreased activation in patients with OCD and their unaffected close relatives compared to controls during reversal learning (Chamberlain and others 2008). Additionally, increased functional connectivity of a nearby region of BA 10 in OCD patients has been associated with a reduction in subclinical OCD symptoms after fMRI neurofeedback training, using activity in BA 10 as the neurofeedback signal (Scheinost and others 2014).

A region of the anterior cingulate cortex (ACC) (MNI coordinate of peak voxel: +3, +32, +10) is additionally implicated in computing the difference in reliability between the goal-oriented and habitual control systems (Lee and others 2014). Such a role for the ACC is consistent with widely held theories of ACC function, which propose that the ACC monitors conflicts in information processing (Botvinick and others 2004; Ridderinkhof and others 2004) and evaluates action outcomes (Lee and others 2012; Matsumoto and others 2003; Rushworth and others 2004). The ACC has been proposed to allocate cognitive control

based on the expected payoff from a controlled process, the amount of control necessary to achieve the payoff, and the cost in terms of cognitive effort (Shenhav and others 2013).

Abnormalities of the ACC have been consistently demonstrated in OCD. These include reductions in gray matter (Radua and Mataix-Cols 2009; Rotge and others 2009), hyperactivity at rest (Maia and others 2008), increased activation during symptom provocation (Maia and others 2008), and increased activation during conflict monitoring (Del Casale and others 2011). More recent studies have characterized abnormalities in OCD patients in ACC functional connectivity (Cheng and others 2013; Cocchi and others 2012; Fitzgerald and others 2011; Gruner and others 2014; Hou and others 2012; Posner and others 2013; Yang and others 2010) and integrity of the associated white matter of the cingulum bundle (Cannistraro and others 2007; Gruner and others 2012; Koch and others 2014; Szeszko and others 2005).

The region of the ACC implicated in arbitration (Lee and others 2014) is on the border between what have been traditionally defined as dorsal “cognitive” and rostral/ventral “emotional” ACC (Bush and others 2000). Functional abnormalities of both the dorsal (Huyser and others 2010; Koch and others 2012) and rostral/ventral regions (Fitzgerald and others 2005; Huyser and others 2011; Yucel and others 2007) of the ACC have been identified in OCD. Recent meta-analytic research suggests a functionally integrated view of the ACC (Shackman and others 2011). In fact, studies of negative affect, pain, and cognitive control consistently activate an overlapping region within the rostral portion of dorsal ACC, known as the anterior midcingulate cortex (aMCC), which appears to be sensitive to certainty about actions and outcomes (Shackman and others 2011). This region has been proposed to play a role in engaging control processes in the face of uncertainty (Behrens and others 2007; Shackman and others 2011). This portion of the ACC is the neurosurgical target for cingulotomy (Rauch and others 2000), a treatment option for patients with severe treatment-refractory OCD (Dougherty and others 2002). It has been shown to exhibit abnormal functional coupling to the ventral striatum, including ventral putamen and ventral head of the caudate, in OCD patients anticipating punishment (Beucke and others 2012).

This conjunction of neuroimaging findings suggests that abnormalities within the ACC may also contribute to the cognitive inflexibility observed in OCD patients. The implicated region of aMCC may synthesize information, including differential reinforcement of alternative decision-making strategies, into a biasing signal (Shackman and others 2011). Disruption of this signal would impair efficient arbitration and might contribute to functional deficits of the arbitration signal in the ilPFC and FPC.

Delineation of the mechanisms and substrates of arbitration between model-free and model-based behavioral control is a new area of research (Lee and others, 2014), and no studies have directly addressed these matters in subjects with OCD. Examination of the specific brain areas identified as involved in the mechanisms of arbitration may provide correlative evidence in favor of our hypothesis (c.f. Figure 2). A more direct test will require the use of sophisticated behavioral tasks such as that used by Lee and others (2014) to directly examine the capacities for real-time arbitration between action strategies, and their neural correlates, in patients. The strongest support for our hypothesis would be if weak arbitration could be

shown to correlate directly with measures of compulsions, or of symptomatology more generally.

Conclusion and implications for treatment

Behavioral and neural system dysfunction on measures of set shifting in both probands with OCD and unaffected first degree relatives (Chamberlain and others 2007; Chamberlain and others 2008; Viswanath and others 2009) has led to the idea that a general propensity toward rigid, inflexible behavior is a cognitive endophenotype for the disorder. We propose that cognitive inflexibility in OCD may be best understood as reflecting a deficit in the mechanisms of arbitration between habitual control (model-free reinforcement learning) and goal-oriented control (model-based reinforcement learning). Habitual control is likely to be the brain's default computational regime, at least in the context of reinforced learning (Lee and others 2014), with deviations from habitual behavior and the initiation of goal-directed processes requiring the recruitment of additional regions involved in cognitive control. A deficit in arbitration between these systems might lead to changes in the overall configuration of the systems over time in patients with OCD.

Recent findings regarding the neural substrates underlying this ability to dynamically and flexibly switch between habitual and goal-oriented control systems implicate the anterior iLPFC, FPC, and ACC (Lee and others 2014), brain regions that are functionally abnormal in OCD patients. We highlight evidence of reduced functional connectivity of anterior iLPFC in OCD patients, both globally and specifically with the dorsal putamen (Anticevic and others 2014; Harrison and others 2009), which suggests an impairment of its regulation of circuits associated with model-free control of behavior. We underscore abnormalities in OCD patients of aMCC, a region of the ACC particularly implicated in monitoring the degree of uncertainty involved in an instrumental action or behavioral outcome and subsequently signal other brain regions to implement goal-directed control (Shackman and others 2011).

A focus on the neural mechanisms of arbitration has the potential to inform treatment. The gold standard for cognitive behavioral treatment (CBT) of OCD is the technique of exposure with response prevention (ERP). ERP involves exposing an individual to his or her fear (the obsessive thought and/or the environmental cues that trigger it), while preventing the individual from engaging in the compulsive behavior that he or she typically performs to reduce anxiety. ERP has traditionally been thought to work by way of the habituation that takes place when a patient is exposed to the anxiety provoking cue for an extended period of time (while refraining from compulsive behaviors to bring the anxiety down) and the extinction learning that takes place as the person sees that the imagined feared consequence does not occur. An alternative way to understand the efficacy of ERP, which is not mutually exclusive, is that it assists patients in breaking compulsions (i.e. maladaptive habits, or model-free behavior) and using new, more adaptive (goal-directed, model-based) behaviors. Dual learning systems theory suggests that refraining from a compulsive act (an existing habit) requires utilizing the parallel model based/ goal directed system; the perspective developed by Lee and others (2014) and above suggests that this switch necessarily depends on the arbitration system (see Figure 1). An important mechanism of change in the ERP process, in addition to extinction, may thus be exercising this arbitration system. ERP

accomplishes this outcome by confronting a patient's specific OCD symptoms, requiring them to tolerate anxiety-eliciting situations as they learn to shift between neural systems and exercise executive control in the face of the distressing cue. The patient is, thus, required to shift between neural systems, a mechanism which we hypothesize may be a locus of pathology of these individuals, while in a highly anxious state.

An alternative therapeutic approach would be to strengthen the mechanism of shifting between neural systems in the absence of symptom provocation. Cognitive remediation therapy (CRT) (Keshavan and others 2014) may be useful in this context as an adjunct or precursor to CBT. CRT is a type of rehabilitation treatment designed to harness plasticity and improve neurocognitive abilities. Contemporary models of cognitive remediation propose that repeated cognitive exercises improve neurocognitive function by modifying the activity level of brain systems that have been performing aberrantly (Bell and others 2001; Wexler and others 2000). CRT designed to gradually strengthen ability to flexibly switch between habitual and goal-oriented control system, independent of the symptom provocation that is inherent to ERP, may thus have therapeutic potential and merit further development.

References

- Abramowitch A, Abramowitz JS, Mittelman A. The neuropsychology of adult obsessive-compulsive disorder: A meta-analysis. *Clin Psychol Rev.* 2013; 33:1163–71. [PubMed: 24128603]
- Ahmari SE, Spellman T, Douglass NL, Kheibek MA, Simpson HB, Deisseroth K. Repeated corticostriatal stimulation stimulates persistent OCD-like behavior. *Science.* 2013; 340:1234–9. others. [PubMed: 23744948]
- Anticevic A, Hu S, Zhang S, Savic A, Billingslea E, Wasylink S. Global resting-state functional magnetic resonance imaging analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder. *Biol Psychiatry.* 2014; 75(8):595–605. others. [PubMed: 24314349]
- Balleine BW, Dickinson A. Goal-directed instrumental action: contingency and incentive learning and their cortical substrates. *Neuropharmacology.* 1998; 37(4-5):407–19. [PubMed: 9704982]
- Behrens TE, Woolrich MW, Walton ME, Rushworth MF. Learning the value of information in an uncertain world. *Nat Neurosci.* 2007; 10(9):1214–21. [PubMed: 17676057]
- Bell M, Bryson G, Greig T, Corcoran C, Wexler BE. Neurocognitive enhancement therapy with work therapy: effects on neuropsychological test performance. *Arch Gen Psychiatry.* 2001; 58(8):763–8. [PubMed: 11483142]
- Beucke JC, Kaufmann C, Linnman C, Gruetzmann R, Endrass T, Deckersbach T. Altered cingulo-striatal coupling in obsessive-compulsive disorder. *Brain Connect.* 2012; 2(4):191–202. others. [PubMed: 22823561]
- Botvinick MM, Cohen JD, Carter CS. Conflict monitoring and anterior cingulate cortex: an update. *Trends Cogn Sci.* 2004; 8(12):539–46. [PubMed: 15556023]
- Burguière E, Monteiro P, Feng G, Graybiel AM. Optogenetic stimulation of lateral orbitofrontal-striatal pathway suppresses compulsive behavior. *Science.* 2013; 340:1243–6. [PubMed: 23744950]
- Bush G, Luu P, Posner MI. Cognitive and emotional influences in anterior cingulate cortex. *Trends Cogn Sci.* 2000; 4(6):215–222. [PubMed: 10827444]
- Cannistraro PA, Makris N, Howard JD, Wedig MM, Hodge SM, Wilhelm S. A diffusion tensor imaging study of white matter in obsessive-compulsive disorder. *Depress Anxiety.* 2007; 24(6):440–6. others. [PubMed: 17096398]
- Chamberlain SR, Fineberg NA, Menzies LA, Blackwell AD, Bullmore ET, Robbins TW. Impaired cognitive flexibility and motor inhibition in unaffected first-degree relatives of patients with obsessive-compulsive disorder. *Am J Psychiatry.* 2007; 164(2):335–8. others. [PubMed: 17267798]

- Chamberlain SR, Menzies L, Hampshire A, Suckling J, Fineberg NA, del Campo N. Orbitofrontal dysfunction in patients with obsessive-compulsive disorder and their unaffected relatives. *Science*. 2008; 321(5887):421–2. others. [PubMed: 18635808]
- Cheng Y, Xu J, Nie B, Luo C, Yang T, Li H. Abnormal resting-state activities and functional connectivities of the anterior and the posterior cortex in medication-naïve patients with obsessive-compulsive disorder. *PLoS One*. 2013; 8(6):e67478. others. [PubMed: 23840714]
- Cocchi L, Harrison BJ, Pujol J, Harding IH, Fornito A, Pantelis C. Functional alterations of large-scale brain networks related to cognitive control in obsessive-compulsive disorder. *Hum Brain Mapp*. 2012; 33(5):1089–106. others. [PubMed: 21612005]
- Daw ND, Gershman SJ, Seymour B, Dayan P, Dolan RJ. Model-based influences on humans' choices and striatal prediction errors. *Neuron*. 2011; 69(6):1204–15. [PubMed: 21435563]
- Daw ND, Niv Y, Dayan P. Uncertainty-based competition between prefrontal and dorsolateral striatal systems for behavioral control. *Nat Neurosci*. 2005; 8(12):1704–11. [PubMed: 16286932]
- Deckersbach T, Savage CR, Curran T, Bohné A, Wilhelm S, Baer L. A study of parallel implicit and explicit information processing in patients with obsessive-compulsive disorder. *Am J Psychiatry*. 2002; 159(10):1780–2. others. [PubMed: 12359688]
- Del Casale A, Kotzalidis GD, Rapinesi C, Serata D, Ambrosi E, Simonetti A. Functional neuroimaging in obsessive-compulsive disorder. *Neuropsychobiology*. 2011; 64(2):61–85. others. [PubMed: 21701225]
- Dezfouli A, Balleine BW. Habits, action sequences and reinforcement learning. *Eur J Neurosci*. 2012; 35(7):1036–51. [PubMed: 22487034]
- Doll BB, Shohamy D, Daw ND. Multiple memory systems as substrates for multiple decision systems. *Neurobiol Learn Mem*. 2014
- Dougherty DD, Baer L, Cosgrove GR, Cassem EH, Price BH, Nierenberg AA. Prospective long-term follow-up of 44 patients who received cingulotomy for treatment-refractory obsessive-compulsive disorder. *Am J Psychiatry*. 2002; 159(2):269–75. others. [PubMed: 11823270]
- Fineberg NA, Potenza MN, Chamberlain SR, Berlin HA, Menzies L, Bechara A. Probing compulsive and impulsive behaviors, from animal models to endophenotypes: a narrative review. *Neuropsychopharmacology*. 2010; 35(3):591–604. others. [PubMed: 19940844]
- Fitzgerald KD, Welsh RC, Gehring WJ, Abelson JL, Himle JA, Liberzon I. Error-related hyperactivity of the anterior cingulate cortex in obsessive-compulsive disorder. *Biol Psychiatry*. 2005; 57(3):287–94. others. [PubMed: 15691530]
- Fitzgerald KD, Welsh RC, Stern ER, Angstadt M, Hanna GL, Abelson JL. Developmental alterations of frontal-striatal-thalamic connectivity in obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 2011; 50(9):938–948. e3. others. [PubMed: 21871375]
- Gillan CM, Morein-Zamir S, Urcelay GP, Sule A, Voon V, Apergis-Schoute AM. Enhanced avoidance habits in obsessive-compulsive disorder. *Biol Psychiatry*. 2014; 75(8):631–8. others. [PubMed: 23510580]
- Gillan CM, Papmeyer M, Morein-Zamir S, Sahakian BJ, Fineberg NA, Robbins TW. Disruption in the balance between goal-directed behavior and habit learning in obsessive-compulsive disorder. *Am J Psychiatry*. 2011; 168(7):718–26. others. [PubMed: 21572165]
- Gillan CM, Robbins TW. Goal-directed learning and obsessive-compulsive disorder. *Philos Trans R Soc Lond B Biol Sci*. 2014; 369(1655)
- Graybiel AM. Habits, rituals, and the evaluative brain. *Annual Review of Neuroscience*. 2008; 31:359–87.
- Gruner P, Vo A, Argyelan M, Ikuta T, Degnan AJ, John M. Independent component analysis of resting state activity in pediatric obsessive-compulsive disorder. *Hum Brain Mapp*. 2014 others.
- Gruner P, Vo A, Ikuta T, Mahon K, Peters BD, Malhotra AK. White matter abnormalities in pediatric obsessive-compulsive disorder. *Neuropsychopharmacology*. 2012; 37(12):2730–9. others. [PubMed: 22871914]
- Gu BM, Park JY, Kang DH, Lee SJ, Yoo SY, Jo HJ. Neural correlates of cognitive inflexibility during task-switching in obsessive-compulsive disorder. *Brain*. 2008; 131(Pt 1):155–64. others. [PubMed: 18065438]

- Harrison BJ, Soriano-Mas C, Pujol J, Ortiz H, Lopez-Sola M, Hernandez-Ribas R. Altered corticostriatal functional connectivity in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2009; 66(11):1189–200. others. [PubMed: 19884607]
- Hitchcott PK, Quinn JJ, Taylor JR. Bidirectional modulation of goal-directed actions by prefrontal cortical dopamine. *Cerebral Cortex*. 2007; 17:2820–7. [PubMed: 17322558]
- Hou J, Wu W, Lin Y, Wang J, Zhou D, Guo J. Localization of cerebral functional deficits in patients with obsessive-compulsive disorder: a resting-state fMRI study. *J Affect Disord*. 2012; 138(3): 313–21. others. [PubMed: 22331021]
- Huyser C, Veltman DJ, Wolters LH, de Haan E, Boer F. Functional magnetic resonance imaging during planning before and after cognitive-behavioral therapy in pediatric obsessive-compulsive disorder. *J Am Acad Child Adolesc Psychiatry*. 2010; 49(12):1238–48. 1248, e1–5. [PubMed: 21093773]
- Huyser C, Veltman DJ, Wolters LH, de Haan E, Boer F. Developmental aspects of error and high-conflict-related brain activity in pediatric obsessive-compulsive disorder: a fMRI study with a Flanker task before and after CBT. *J Child Psychol Psychiatry*. 2011; 52(12):1251–60. [PubMed: 21793825]
- Joel D, Zohar O, Afek M, Hermesh H, Lerner L, Kuperman R. Impaired procedural learning in obsessive-compulsive disorder and Parkinson's disease, but not in major depressive disorder. *Behav Brain Res*. 2005; 157(2):253–63. others. [PubMed: 15639176]
- Keshavan MS, Vinogradov S, Rumsey J, Sherrill J, Wagner A. Cognitive training in mental disorders: update and future directions. *Am J Psychiatry*. 2014; 171(5):510–22. [PubMed: 24700194]
- Kessler RC, Petukhova M, Sampson NA, Zaslavsky AM, Wittchen HU. Twelve-month and lifetime prevalence and lifetime morbid risk of anxiety and mood disorders in the United States. *Int J Methods Psychiatr Res*. 2012; 21:169–184. [PubMed: 22865617]
- Koch K, Reess TJ, Rus OG, Zimmer C, Zaudig M. Diffusion tensor imaging (DTI) studies in patients with obsessive-compulsive disorder (OCD): A review. *J Psychiatr Res*. 2014
- Koch K, Wagner G, Schachtzabel C, Peikert G, Schultz CC, Sauer H. Aberrant anterior cingulate activation in obsessive-compulsive disorder is related to task complexity. *Neuropsychologia*. 2012; 50(5):958–64. others. [PubMed: 22349440]
- Koran LM. Quality of life in obsessive-compulsive disorder. *Psychiatr Clin North Am*. 2000; 23(3): 509–17. [PubMed: 10986724]
- Lee AS, Duman RS, Pittenger C. A double dissociation revealing bidirectional competition between striatum and hippocampus during learning. *Proc Natl Acad Sci U S A*. 2008; 105(44):17163–8. [PubMed: 18955704]
- Lee D, Seo H, Jung MW. Neural basis of reinforcement learning and decision making. *Annu Rev Neurosci*. 2012; 35:287–308. [PubMed: 22462543]
- Lee SW, Shimojo S, O'Doherty JP. Neural computations underlying arbitration between model-based and model-free learning. *Neuron*. 2014; 81(3):687–99. [PubMed: 24507199]
- Liu H, Qin W, Li W, Fan L, Wang J, Jiang T. Connectivity-based parcellation of the human frontal pole with diffusion tensor imaging. *J Neurosci*. 2013; 33(16):6782–90. others. [PubMed: 23595737]
- Maia TV, Cooney RE, Peterson BS. The neural bases of obsessive-compulsive disorder in children and adults. *Dev Psychopathol*. 2008; 20(4):1251–83. [PubMed: 18838041]
- Matsumoto K, Suzuki W, Tanaka K. Neuronal correlates of goal-based motor selection in the prefrontal cortex. *Science*. 2003; 301(5630):229–32. [PubMed: 12855813]
- Poldrack RA, Clark J, Pare-Blagoev EJ, Shohamy D, Creso Moyano J, Myers C. Interactive memory systems in the human brain. *Nature*. 2001; 414(6863):546–50. others. [PubMed: 11734855]
- Posner J, Marsh R, Maia TV, Peterson BS, Gruber A, Simpson HB. Reduced functional connectivity within the limbic cortico-striato-thalamo-cortical loop in unmedicated adults with obsessive-compulsive disorder. *Hum Brain Mapp*. 2013
- Quinn JJ, Pittenger C, Lee AS, Pierson JL, Taylor JR. Striatum-dependent habits are insensitive to both increases and decreases in reinforcer value in mice. *Eur J Neurosci*. 2013; 37(6):1012–21. [PubMed: 23298231]
- Radua J, Mataix-Cols D. Voxel-wise meta-analysis of grey matter changes in obsessive-compulsive disorder. *Br J Psychiatry*. 2009; 195(5):393–402. [PubMed: 19880927]

- Rauch SL, Kim H, Makris N, Cosgrove GR, Cassem EH, Savage CR. Volume reduction in the caudate nucleus following stereotactic placement of lesions in the anterior cingulate cortex in humans: a morphometric magnetic resonance imaging study. *J Neurosurg.* 2000; 93(6):1019–25. others. [PubMed: 11117844]
- Rauch SL, Savage CR, Alpert NM, Dougherty D, Kendrick A, Curran T. Probing striatal function in obsessive-compulsive disorder: a PET study of implicit sequence learning. *J Neuropsychiatry Clin Neurosci.* 1997; 9(4):568–73. others. [PubMed: 9447498]
- Rauch SL, Wedig MM, Wright CI, Martis B, McMullin KG, Shin LM. Functional magnetic resonance imaging study of regional brain activation during implicit sequence learning in obsessive-compulsive disorder. *Biol Psychiatry.* 2007; 61(3):330–6. others. [PubMed: 16497278]
- Remijnse PL, Nielen MM, van Balkom AJ, Cath DC, van Oppen P, Uylings HB. Reduced orbitofrontal-striatal activity on a reversal learning task in obsessive-compulsive disorder. *Arch Gen Psychiatry.* 2006; 63(11):1225–36. others. [PubMed: 17088503]
- Ridderinkhof KR, Ullsperger M, Crone EA, Nieuwenhuis S. The role of the medial frontal cortex in cognitive control. *Science.* 2004; 306(5695):443–7. [PubMed: 15486290]
- Rotge JY, Guehl D, Dilharreguy B, Tignol J, Bioulac B, Allard M. Meta-analysis of brain volume changes in obsessive-compulsive disorder. *Biol Psychiatry.* 2009; 65(1):75–83. others. [PubMed: 18718575]
- Ruscio AM, Stein DJ, Chiu WT, Kessler RC. The epidemiology of obsessive-compulsive disorder in the National Comorbidity Survey Replication. *Mol Psychiatry.* 2010; 15:53–63. [PubMed: 18725912]
- Rushworth MF, Walton ME, Kennerley SW, Bannerman DM. Action sets and decisions in the medial frontal cortex. *Trends Cogn Sci.* 2004; 8(9):410–7. [PubMed: 15350242]
- Scheinost D, Stoica T, Wasylink S, Gruner P, Saksa J, Pittenger C. Resting state functional connectivity predicts neurofeedback response. *Front Behav Neurosci.* 2014; 8(338) others.
- Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ. The integration of negative affect, pain and cognitive control in the cingulate cortex. *Nat Rev Neurosci.* 2011; 12(3):154–67. [PubMed: 21331082]
- Shenhav A, Botvinick MM, Cohen JD. The expected value of control: an integrative theory of anterior cingulate cortex function. *Neuron.* 2013; 79(2):217–40. [PubMed: 23889930]
- Shin NY, Lee TY, Kim E, Kwon JS. Cognitive functioning in obsessive-compulsive disorder: a meta-analysis. *Psychol Med.* 2014; 44:1121–30. [PubMed: 23866289]
- Simon DA, Daw ND. Neural correlates of forward planning in a spatial decision task in humans. *J Neurosci.* 2011; 31(14):5526–39. [PubMed: 21471389]
- Smith KS, Graybiel AM. A dual operator view of habitual behavior reflecting cortical and striatal dynamics. *Neuron.* 2013; 79:361–74. [PubMed: 23810540]
- Szeszko PR, Ardekani BA, Ashtari M, Malhotra AK, Robinson DG, Bilder RM. White matter abnormalities in obsessive-compulsive disorder: a diffusion tensor imaging study. *Arch Gen Psychiatry.* 2005; 62(7):782–90. others. [PubMed: 15997020]
- Tanaka SC, Balleine BW, O'Doherty JP. Calculating consequences: brain systems that encode the causal effects of actions. *J Neurosci.* 2008; 28(26):6750–5. [PubMed: 18579749]
- Valentin VV, Dickinson A, O'Doherty JP. Determining the neural substrates of goal-directed learning in the human brain. *J Neurosci.* 2007; 27(15):4019–26. [PubMed: 17428979]
- van den Heuvel OA, Remijnse PL, Mataix-Cols D, Vrenken H, Groenewegen HJ, Uylings HB. The major symptom dimensions of obsessive-compulsive disorder are mediated by partially distinct neural systems. *Brain.* 2009; 132(Pt 4):853–68. others. [PubMed: 18952675]
- Vincent JL, Kahn I, Snyder AZ, Raichle ME, Buckner RL. Evidence for a frontoparietal control system revealed by intrinsic functional connectivity. *J Neurophysiol.* 2008; 100(6):3328–42. [PubMed: 18799601]
- Viswanath B, Janardhan Reddy YC, Kumar KJ, Kandavel T, Chandrashekar CR. Cognitive endophenotypes in OCD: a study of unaffected siblings of probands with familial OCD. *Prog Neuropsychopharmacol Biol Psychiatry.* 2009; 33(4):610–5. [PubMed: 19272409]
- Voon V, Derbyshire K, Ruck C, Irvine MA, Worbe Y, Enander J. Disorders of compulsivity: a common bias towards learning habits. *Mol Psychiatry.* 2014 others.

- Wexler BE, Anderson M, Fulbright RK, Gore JC. Preliminary evidence of improved verbal working memory performance and normalization of task-related frontal lobe activation in schizophrenia following cognitive exercises. *Am J Psychiatry*. 2000; 157(10):1694–7. [PubMed: 11007730]
- Yang T, Cheng Y, Li H, Jiang H, Luo C, Shan B. Abnormal regional homogeneity of drug-naïve obsessive-compulsive patients. *Neuroreport*. 2010; 21(11):786–90. others. [PubMed: 20571458]
- Yeo BT, Krienen FM, Sepulcre J, Sabuncu MR, Lashkari D, Hollinshead M. The organization of the human cerebral cortex estimated by intrinsic functional connectivity. *J Neurophysiol*. 2011; 106(3):1125–65. others. [PubMed: 21653723]
- Yin HH, Knowlton BJ, Balleine BW. Blockade of NMDA receptors in the dorsomedial striatum prevents action-outcome learning in instrumental conditioning. *Eur J Neurosci*. 2005; 22(2):505–12. [PubMed: 16045503]
- Yin HH, Knowlton BJ, Balleine BW. Inactivation of dorsolateral striatum enhances sensitivity to changes in the action-outcome contingency in instrumental conditioning. *Behav Brain Res*. 2006; 166(2):189–96. [PubMed: 16153716]
- Yucel M, Harrison BJ, Wood SJ, Fornito A, Wellard RM, Pujol J. Functional and biochemical alterations of the medial frontal cortex in obsessive-compulsive disorder. *Arch Gen Psychiatry*. 2007; 64(8):946–55. others. [PubMed: 17679639]

Figure 1.

A schematic representation of the arbitration between model-free and model-based learning during reinforced learning, as suggested by Lee et al (Lee and others 2014).

Figure 2.

Clusters where OCD patients showed significantly decreased whole-brain GBC connectivity relative to healthy controls. This pattern was centered on inferior lateral prefrontal cortex (ilPFC), left middle frontal gyrus, and precentral gyrus. From Anticevic and others 2014.

Figure 3.

(A) We examined the pattern of functional connectivity in a sample of healthy adults (N=96) from the left ilPFC region implicated in OCD [Anticevic and others 2014]. This area is functionally connected both to the frontal control network and to elements of the default-mode network, such as the lateral temporal lobe. In contrast, the ilPFC seed exhibits negative functional connectivity with primary sensory cortices. (B) We juxtaposed the IFG region with a published functional parcellation of the cortex [Yeo and others 2011]. The IFG region identified in our OCD study [Anticevic and others 2014], outlined here in black, overlaps with elements of both the fronto-parietal control system (orange) and the default-mode network (red). This functional area may be uniquely positioned to merge computations across these large-scale networks.