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SPECIAL ARTICLE

Neurocircuit models of obsessive-compulsive disorder: limitations and future directions for research

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Obsessive-compulsive disorder (OCD) is a common psychiatric condition classically characterized by obsessions (recurrent, intrusive and unwanted thoughts) and compulsions (excessive, repetitive and ritualistic behaviors or mental acts). OCD is heterogeneous in its clinical presentation and not all patients respond to first-line treatments. Several neurocircuit models of OCD have been proposed with the aim of providing a better understanding of the neural and cognitive mechanisms involved in the disorder. These models use advances in neuroscience and findings from neuropsychological and neuroimaging studies to suggest links between clinical profiles that reflect the symptoms and experiences of patients and dysfunctions in specific neurocircuits. Several models propose that treatments for OCD could be improved if directed to specific neurocircuit dysfunctions, thereby restoring efficient neurocognitive function and ameliorating the symptomatology of each associated clinical profile. Yet, there are several important limitations to neurocircuit models of OCD. The purpose of the current review is to highlight some of these limitations, including issues related to the complexity of brain and cognitive function, the clinical presentation and course of OCD, etiological factors, and treatment methods proposed by the models. We also provide suggestions for future research to advance neurocircuit models of OCD and facilitate translation to clinical application.

Keywords: Obsessive-compulsive disorder; clinical presentation; neurocircuit models; neurobiology; treatment advances

Introduction

Obsessive-compulsive disorder (OCD) is a common psychiatric condition traditionally described by irrational, unwanted, recurring and intrusive thoughts (obsessions) and excessive, repetitive, ritualistic behaviors, or mental acts (compulsions). However, compulsions can be driven by different types of motivations. Classically, they are performed to relieve uncomfortable feelings generated by obsessions. In this context, uncomfortable feelings are associated, mostly, with fears of contamination or of harm to oneself or others, persistent self-doubt, and intrusive forbidden or taboo thoughts. The consequent repetitive behaviors that produce relief include repetitive

hand-washing, cleaning, checking, and mental rituals such as counting. Nevertheless, compulsive behaviors may also be performed to relieve uncomfortable visual, auditory, or tactile sensations and perceptions that things are not "just-right" or "complete" (sensory phenomena),[1] such as touching an object to achieve a certain tactile sensation or ordering/arranging objects until they look symmetrical or appear "just-right." Due to impairments in the ability to inhibit some of these repetitive behaviors, over time and with repetition, compulsions can also become habitual and are triggered by specific internal or external stimuli.[2] Finally, some compulsions may be driven by feelings of reward.[2]

Obsessions and compulsions are often chronic[3] and lead to significant impairments in social, educational and

occupational functioning and reduced quality of life.[4] The most commonly used treatments for OCD are cognitive behavioral therapy (CBT) and selective serotonin reuptake inhibitor (SSRI) medication, which are effective in significantly reducing the severity of obsessions and compulsions in many patients.[5] Still, even with successful reductions in disease severity, many patients remain with residual symptoms and persistent functional impairments and approximately half of patients do not respond enough to first-line behavioral or pharmacological therapies.[5]

A prominent view in the scientific community is that a better understanding of the neural and cognitive mechanisms involved in OCD could lead to new and effective treatments that more precisely target the neurobiological alterations that underlie obsessions and compulsions.[6] Along these lines, several models based on neuropsychological and neuroimaging findings in OCD have been proposed to highlight dysfunctions in cortico-striatal-thalamic-cortical (CSTC), fronto-limbic, and fronto-parietal circuits involved in the condition[7-9] (summarized in Table 1). We recently extended this work by proposing a neurocircuit-based taxonomy to guide the treatment of OCD based on the idea that clinical profiles, i.e., experiences, symptoms, and neurocognitive alterations, are linked to specific neurocircuits[10] (summarized in Table 1 and illustrated in Figure 1). We suggested different neurocircuit-based treatment options, including CBT and SSRIs, but also novel and potentially more precise neuroscience-based methods (e.g., repetitive transcranial magnetic stimulation [rTMS], functional magnetic resonance imaging [fMRI] neurofeedback) that could be used to target the neurocircuit alterations underlying the different clinical profiles (Table 1 and Figure 1).

These models have been valuable in synthesizing the vast clinical and neuroimaging literature in OCD and in providing testable hypotheses concerning core phenotypic and neurobiological profiles and neurocircuit-based treatment approaches. Yet, there are several crucial limitations to existing neurocircuit models of OCD that should be considered. The purpose of the current review is therefore to critically discuss some of the limitations of these models, including issues related to the complexity of brain and cognitive function, the clinical presentation and course of OCD, etiological factors, and treatment methods proposed by the models, and to highlight directions for future research in the area.

Limitations related to the complexity of brain and cognitive function

A key limitation of neurocircuit models is that they present an over-simplified account of brain and cognitive function. For instance, neurocognitive functions do not neatly map onto discrete neurocircuits as implied in the models. As one example of this, dysregulated fear-like responses to threatening and OCD-provoking stimuli have been associated with overactivity in regions of the fronto-limbic circuit (amygdala and ventromedial prefrontal cortex [vmPFC]) and underactivity in regions of the dorsal cognitive circuit (dorsolateral/dorsomedial prefrontal cortex [dlPFC/dmPFC]),[11,12] brain effects that have been proposed as a key neurocognitive alteration involved in fear-based obsessions in models of OCD (Table 1 and Figure 1). We have therefore suggested that treatments for fear-based obsessions may be optimized by targeting these two neurocircuits, specifically by decreasing fronto-limbic hyperactivity and increasing dorsal cognitive hypoactivity[10] (Table 1 and Figure 1).

However, while meta-analyses have confirmed that dysregulated emotional responses are associated with hyperactivity in fronto-limbic regions in OCD, they also revealed consistent patterns of hyperactivation in other regions, including the insula and temporal and parietal areas.[12,13] These findings indicate that altered activity in a more extended neural network is involved in dysregulated fear in OCD. In line with these findings, meta-analyses of neuroimaging studies in individuals without psychiatric conditions have shown a broad network of regions, including the insula, inferior parietal lobule, inferior temporal gyrus, and inferior frontal gyrus (IFG) to be activated during the processing and regulation of fear and other negative emotions in addition to the amygdala, vmPFC and dorsal prefrontal regions.[14-16] It is therefore difficult to attribute dysregulated fear responses solely to the fronto-limbic circuit, which has implications for models proposing that selectively targeting fronto-limbic circuitry could ameliorate fear-based OCD symptoms.

A related issue is that experimental tasks used to measure neurocognitive functions often do not engage a single neurocognitive process, but multiple processes and multiple underlying neurocircuits. This is true even for very simple and well-designed tasks. For example, the go/nogo task involves pressing a button rapidly to a frequently-presented "go" stimulus and inhibiting the button-press to an infrequent "nogo" stimulus. This task is widely used to measure response inhibition (to the nogo stimulus) in neuroimaging research and has revealed consistent patterns of activation in the IFG on nogo trials compared to go trials; these data have led to the widely-held view that the IFG is a key mediator of response inhibition.[17] Findings of underactivation in the IFG combined with poorer performance on nogo trials of this task have been used to support the proposal in several neurocircuit models that response inhibition impairments associated with hypoactivity in the ventral cognitive circuit (which includes the IFG) is a key dysfunction in OCD (Table 1 and Figure 1). Yet, compared to go trials, nogo trials also more strongly engage other processes, including conflict monitoring.[18,19] Conflict monitoring is responsible for flagging when perception or behavior deviates from what is expected.[18,19] It is mediated largely by the dorsal part of the anterior cingulate cortex (ACC) and is associated with dopaminergic reward signaling in brain regions involved in the ventral affective "reward" circuit.[20] Thus, even a simple task such as the go/nogo involves other neurocognitive functions and neurocircuits beyond those it is designed to measure (i.e., response inhibition). This has implications for neurocircuit models of OCD

Table 1 Summary of neurocircuit-based models of OCD

Author	Overview of the model
Graybiel & Rauch[7]	These authors highlighted the importance of CSTC circuits in the neurobiology of OCD, with particular emphasis on the "OCD circuit" connecting the caudate nucleus, ACC and OFC. The authors linked dysfunctions in the OCD circuit to alterations in executive function, reward processing and habit learning and proposed that these may contribute to the production of obsessive-compulsive symptoms.
Milad & Rauch[8]	These authors extended previous CSTC models and the view that OCD could be considered a disorder of self-regulation and inhibition to highlight the role of the amygdala and the production and regulation of fear in obsessive-compulsive symptomatology. The model linked neurocognitive mechanisms to dysfunctions in three neurocircuits: 1) the "affective circuit," which comprised the ACC/vmPFC, NAcc), and thalamus and was proposed to be involved in processing affect and reward; 2) the "ventral cognitive circuit," which consisted of the anterolateral OFC, putamen and thalamus and was suggested to be involved in motor and response inhibition; 3) the "dorsal cognitive circuit," which included the dlPFC, dorsal caudate, and thalamus and was proposed to mediate working memory and executive function. The authors also discussed the role of interactions between the amygdala and the affective and dorsal cognitive circuits in impaired fear extinction in OCD. Finally, the authors discussed the possibility of targeting these neurocircuits with deep brain stimulation and/or measuring their function as therapeutic markers to improve treatment for OCD.
Van den Heuvel et al.[9]	These authors further elaborated and expanded on Milad and Rauch's[8] model to consider five neurocircuits and associated neurocognitive functions involved in OCD and other disorders characterized by compulsivity. These were: 1) the "sensorimotor CSTC circuit," which includes the SMA, posterior putamen, and thalamus and is involved in stimulus-response based habit behavior; 2) the "dorsal cognitive CSTC circuit," which connects the pre-SMA, dlPFC, dmPFC, dorsal caudate, and thalamus and mediates executive control functions such as working memory, planning and emotion regulation; 3) the "ventral cognitive CSTC circuit," which includes the IFG, vlPFC, ventral caudate, and thalamus and is involved in response inhibition; 4) the "affective CSTC circuit," which connects the OFC, NAcc and thalamus and is involved in stimulus-response based motivational and affective behaviors; 5) the "fronto-limbic circuit," which includes the vmPFC and amygdala, involved in the learning and extinction of fear responses. The model highlights the importance of interactions between the circuits, for example with the dorsal and ventral cognitive control circuits exerting top-down regulation of emotion mediated by the fronto-limbic and affective circuits. The authors also considered neural mechanisms involved in treatments for OCD, including CBT, SSRIs, deep brain stimulation, and non-invasive neuromodulatory techniques (rTMS, tDCS).
Shephard et al.[10]	We recently expanded on van den Heuvel et al.'s[9] model to propose several "clinical profiles" that reflect different phenotypic expressions of OCD, which we derived from patients' reports of their subjective experiences of OCD symptoms. We linked each clinical profile with underlying neurocognitive alterations related to dysfunctions in the five neurocircuits proposed by van den Heuvel et al.,[9] and suggested specific treatment approaches targeting the clinical profiles and neurocircuit dysfunctions that could be tested in future research (illustrated in Figure 1). These clinical profiles were: 1) "dysregulated fear," characterized by excessive and/or inappropriate and poorly controlled physiological fear responses that are associated with obsessions and drive compulsive behaviors, mediated by hyperactive fronto-limbic (amygdala, vmPFC) activity and hypoactive dorsal cognitive circuit top-down control of fear responses; 2) "intolerance of uncertainty," reflecting an inability to cope with uncertainty that contributes to obsessions and repetitive behaviors (e.g., repetitive behaviors to attenuate uncertainty preoccupations), underpinned by hyperactive fronto-limbic circuit activity; 3) "sensory phenomena," i.e., aversive or uncomfortable perceptions or sensations (e.g., the feeling that things are "not just right"; the sensation of feeling dirty) that drive compulsive behaviors, associated with hyperactivity in the sensorimotor circuit as well as the insula; 4) "excessive habit-formation," reflecting long-standing compulsive behaviors, which were initially associated with recurrent and distressful thoughts, ideas or images, but after multiple repetitions, over time, became more automatic, mediated by hyperactivity in the sensorimotor circuit; 5) "impaired response inhibition," i.e., difficulties in preventing inappropriate thoughts or behaviors, linked to hypoactivity in the ventral cognitive circuit; 6) "altered reward responsiveness," reflecting a reduced sensitivity to rewards coupled with exaggerated anticipation of punishments in some patients which leads to feelings of relief/reward obtained by completing compulsive and/or avoidance behaviors, mediated by atypicalities in regional activity and functional connectivity within the ventral affective circuit; 7) "executive dysfunction," including difficulties with planning, working memory, and top-down emotion regulation due to hypoactivity in the dorsal cognitive circuit. In terms of treatment strategies, we proposed that the "dysregulated fear" and "intolerance of uncertainty" profiles may be best treated using therapies that aim to reduce hyperactivity in the fronto-limbic circuit (CBT, SSRIs, amygdala/vmPFC, fMRI neurofeedback, deep brain stimulation targeting the ALIC) and increase hypoactive dorsal cognitive circuit top-down control of the fronto-limbic circuit (CBT, dlPFC rTMS, medial PFC deep-TMS). We suggested that the "sensory phenomena" and "excessive habit-formation" profiles could be addressed by treatments aiming to reduce excessive sensorimotor circuit activity (habit-reversal training, SMA rTMS) and for sensory phenomena only, regulate insula activity (H-coil insula TMS, ondansetron). For the "impaired response inhibition" profile, we proposed treatments aiming to increase ventral cognitive circuit hypoactivity (deep brain stimulation targeting the subthalamic nucleus and ventral capsule/ventral striatum, fMRI neurofeedback of the IFG). For the "altered reward responsiveness" profile, we suggested therapies targeting reward mechanisms of the ventral affective circuit (SSRIs, dopamine-acting medications such as methylphenidate, fMRI neurofeedback of the NAcc, deep brain stimulation targeting the NAcc). Finally, we suggested that treatment approaches for the "executive dysfunction" profile would involve increasing hypoactivity in the dorsal cognitive circuit (CBT, methylphenidate, dlPFC, and pre-SMA rTMS or tDCS). Evidence for and against each of these neurocircuit-based treatments is discussed in detail in the publication presenting the model.[10]

ACC = anterior cingulate cortex; ALIC = anterior limb of the internal capsule; CBT = cognitive behavioral therapy; CSTC = cortico-striatal-thalamo-cortical; dlPFC = dorsolateral prefrontal cortex; dmPFC = dorsomedial prefrontal cortex; fMRI = functional magnetic resonance imaging; IFG = inferior frontal gyrus; NAcc = nucleus accumbens; OCD = obsessive-compulsive disorder; OFC = orbitofrontal cortex; rTMS = repetitive transcranial magnetic stimulation; SMA = supplementary motor area; SSRIs = selective serotonin reuptake inhibitors; tDCS = transcranial direct current stimulation; vlPFC = ventrolateral prefrontal cortex; vmPFC = ventromedial prefrontal cortex.
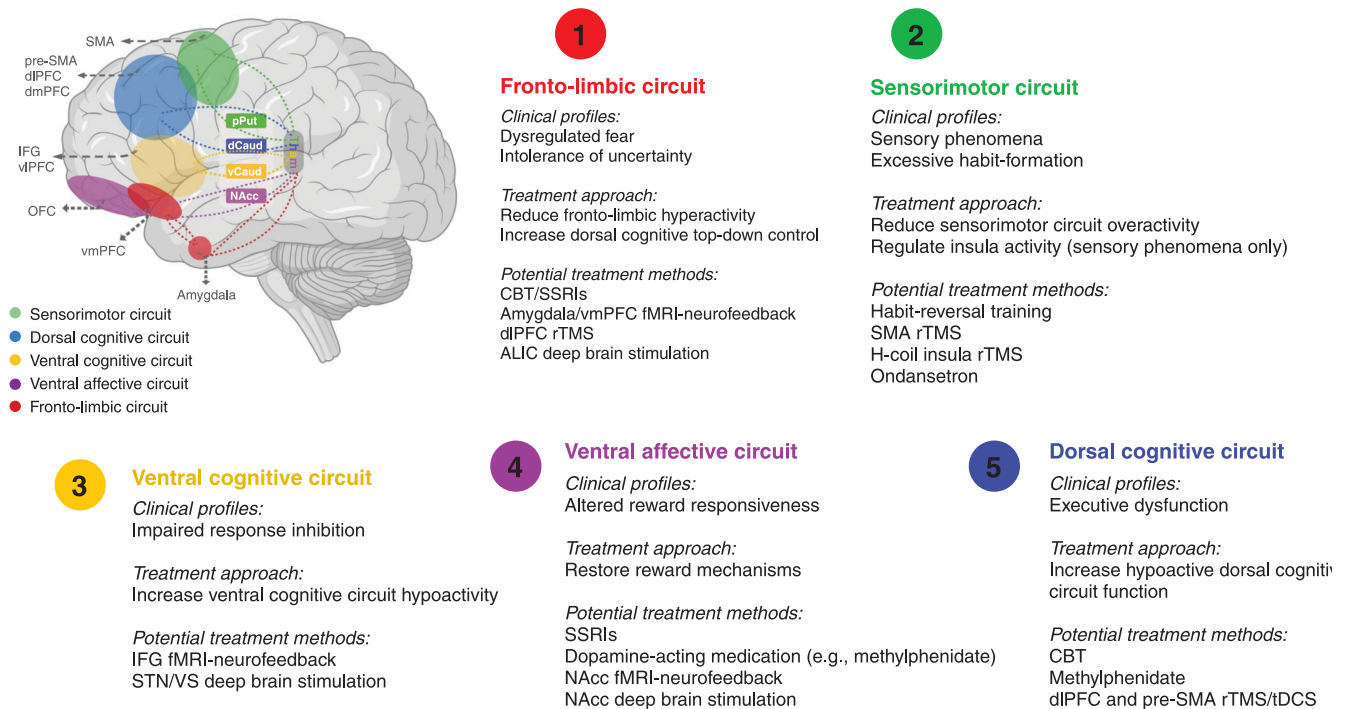
Figure 1 Overview of the neurocircuit-based taxonomy to guide treatment for OCD proposed by Shephard et al.[10] The figure shows the five neurocircuits implicated in OCD and their associated clinical profiles and suggested treatment approaches outlined by Shephard et al.[10] ALIC = anterior limb of the internal capsule; CBT = cognitive behavioral therapy; dCaud = dorsal caudate nucleus; dlPFC/dmPFC = dorsolateral/dorsomedial prefrontal cortex; fMRI = functional magnetic resonance imaging; IFG = inferior frontal gyrus; NAcc = nucleus accumbens; OCD = obsessive-compulsive disorder; OFC = orbitofrontal cortex; Pput = posterior putamen; rTMS = repetitive transcranial magnetic stimulation; SMA = supplementary motor area; SSRIs = selective serotonin reuptake inhibitors; STN/VS = subthalamic nucleus/ventral striatum; tDCS = transcranial direct current stimulation; vCaud = ventral caudate nucleus; vlPFC = ventrolateral prefrontal cortex; vmPFC = ventromedial prefrontal cortex.

because findings from research using a particular task may not reflect only the neurocognitive and neurocircuit alterations purportedly engaged by that task.

This issue is further complicated by the low test-retest reliability of neurocognitive tasks used in fMRI studies to engage specific brain regions, i.e., the same individual performing the task twice may activate different brain regions across assessments. Elliott et al.[21] have recently demonstrated using both meta-analysis and analysis of empirical data that neurocognitive tasks measuring emotion, social cognition, inhibition, executive function, reward, and even simple motor response production were poor at eliciting consistent patterns of activation in the same brain regions across repeated fMRI assessments in the same individuals, all of whom were without psychiatric conditions. The authors therefore concluded that currently used fMRI tasks do not have sufficient test-retest reliability to be used for mapping associations between brain and behavior, nor as biomarkers in the search for the neurobiological basis of psychiatric conditions.[21]

Finally, the vast majority of research cited in support of neurocircuit models of OCD has used the MRI/fMRI technique, while findings from other methods of investigating brain function such as electroencephalography (EEG) and magnetoencephalography (MEG) have rarely been considered. This is important because EEG studies have revealed a robust neural alteration associated with OCD, i.e., increased amplitude of the error-related negativity (ERN) component during error processing in OCD.[22] Evidence indicates that the ERN is generated by the ACC and reflects an error detection mechanism that flags mistakes in behavior that should be corrected (this component is similar to the N2 conflict monitoring component discussed above).[23] The consistency in findings of increased ERN in OCD in both individual studies and meta-analyses suggests that enhanced error monitoring may be an important mechanism involved in the disorder. Yet, these findings have generally not been incorporated in neurocircuit models of OCD (Table 1).

One reason for this may be that the neurocircuit dysfunctions underlying enhanced ERN in OCD are unclear. The ventral affective[23,24] or ventral cognitive[24,25] circuits may be involved, but this is difficult to infer from EEG findings given the low spatial resolution of EEG. fMRI studies also report increased ACC activity during error monitoring in OCD, but activity alterations extend beyond the ventral affective and ventral cognitive circuits.[24] Further, enhanced ERN is not associated with OCD symptom severity[26] and does not change with successful reduction in symptoms following treatment.[25,27] It is

therefore difficult to know exactly how enhanced error monitoring is involved in the neurobiology of OCD and how, or if, it should be targeted in treatment (but see recent work on ERN reductions following attentional bias training in OCD[28]). Further work integrating ERN findings in neurocircuit models and investigating how enhanced error monitoring relates to the clinical presentation of OCD and potential treatments will be an important step for future research.

Furthermore, unlike fMRI, EEG and MEG can be used to study oscillatory neural activity (the rhythmic activity of populations of neurons) at the scalp (EEG) or within and between cortical areas (MEG). Coordinated oscillatory activity across brain regions is believed to be a key mechanism in neural communication and the formation of functional neural networks[29,30] and is therefore highly relevant for understanding neurobiological mechanisms in psychiatric disorders. Indeed, EEG/MEG research has revealed patterns of oscillatory neural network alterations in several psychiatric conditions, which has led to the development and testing of novel treatments designed to target those alterations. For instance, consistent findings of hypoconnected networks mediated by high-frequency gamma oscillations involved in perceptual and cognitive integration have been reported in schizophrenia[31,32] and have been linked with underlying imbalances in excitatory glutamatergic and inhibitory GABAergic neurotransmission.[33] Consequently, novel pharmacological treatment approaches aimed at restoring excitatory/inhibitory signaling have been investigated in schizophrenia and were shown to reduce psychotic symptoms and restore oscillatory gamma hypoactivity.[34-36] Furthermore, EEG/MEG neurofeedback targeted at increasing hypoactive gamma oscillations has been tested in schizophrenia and was shown to improve some of the cognitive deficits associated with the disorder.[37] Despite the richness of information and therapeutic advances yielded by EEG/MEG studies in other disorders, relatively few studies have investigated oscillatory activity in OCD,[38] and the most methodologically rigorous studies have focused on oscillatory mechanisms associated with deep brain stimulation in treatment-refractory patients.[39,40] There is therefore a need for further studies examining oscillatory neural communication in OCD and for the findings to be incorporated in neurobiological models of the disorder.

Limitations related to the clinical presentation and course of OCD

Several further limitations to neurocircuit models are that they do not address the complexities in the clinical presentation of OCD. Specifically, the models consider neurocognitive mechanisms and treatment strategies for an individual clinical profile associated with a particular neurocircuit. For example, in our model we suggested that sensory phenomena, which precede compulsions in some patients, are linked to hyperactivity in the sensorimotor circuit[10] (Table 1 and Figure 1). In the real world, however, clinical profiles and, consequently, their

underlying neurocircuit dysfunctions, co-occur in the same individual at the same time. For instance, the same patient may experience sensory phenomena driven by sensorimotor circuit overactivity and concurrent fear-based obsessions driven by dysregulated fronto-limbic fear responses. In support, a recent study examining subjective experiences of motivations behind OCD symptoms found that a large proportion (56%) of patients reported both feelings of incompleteness (sensory phenomena profile) and fear-of-harm (dysregulated fear profile) to drive their obsessive-compulsive behaviors, while ⩽ 25% reported only fear or only incompleteness motivations.[41] Mataix-Cols et al.[42] also showed that, within a single fMRI scanning session, the same patients showed different neurocircuit dysfunctions depending on the type of OCD symptom provoked, with hyperactivity in vmPFC (fronto-limbic circuit) during washing symptom provocation and altered activity in dorsal cortical regions (dorsal cognitive circuit) during checking symptom provocation.

Neurocircuit models also often do not consider the presence of co-occurring psychiatric conditions, such as depression, anxiety, and chronic tic disorders, such as Tourette syndrome, which manifest in a large proportion of OCD patients.[43,44] These disorders are themselves associated with neurocognitive alterations linked to neurocircuit dysfunctions, which may introduce or complicate the presentation of neurocircuit-based clinical profiles and treatment approaches in OCD. Indeed, experimental studies and comparative meta-analyses suggest that OCD and other co-occurring mental disorders are mediated by distinct but also common neural substrates.[45-50] For instance, Radua et al.[45] reported shared gray matter volume reductions in dorsal anterior cingulate and dorsomedial frontal gyri in patients with OCD and other anxiety disorders compared to non-psychiatric volunteers, which the authors suggested may reflect common neurobiological alterations associated with emotional processing and regulation difficulties in OCD and anxiety disorders. In contrast, OCD patients showed significantly increased putamen and globus pallidus volumes compared to non-psychiatric controls, while patients with other anxiety disorders showed the opposite pattern.[45]

A recent experimental study reported alterations in functional connectivity of the sensorimotor circuit that were associated with both OCD symptoms and tic symptoms in individuals with Tourette syndrome, suggestive of shared sensorimotor circuit dysfunction between these disorders.[46] Likewise, high scores on an instrument measuring sensory phenomena, which involve subjective experiences preceding repetitive behaviors along the continuum between OCD and Tourette syndrome, have been associated with gray matter volume increases in sensorimotor cortex.[47] Similar findings of shared and distinct neuroanatomical and neurofunctional alterations in regions of the fronto-limbic, sensorimotor, and ventral and dorsal cognitive circuits have been reported in meta-analyses comparing neural correlates of inhibitory control between individuals with OCD and other frequently-co-occurring conditions including autism[48] and attention-deficit/hyperactivity disorder (ADHD).[49] However, a more

recent and larger-scale study comparing brain structure between OCD, ASD, ADHD, and non-psychiatric controls found no overlap in structural alterations between these disorders.[50]

Most neurocircuit models (with the exception of van den Heuvel et al.[9]) do not consider longitudinal changes in OCD symptoms and neurocircuitry across development, i.e., from childhood through adolescence into adulthood and over time in each of these developmental stages. Indeed, compared to the many studies conducted in adults with OCD, considerably fewer have examined the phenomenology and neural basis of OCD symptoms in children. Existing studies indicate that OCD in children and adolescents is phenomenologically similar to that observed in adults, with symptom dimensions of cleaning/contamination, symmetry/ordering, and fear of harm/unacceptable thoughts.[51] Children with OCD are vulnerable to co-occurring conditions, particularly tic disorders,[52] depression and generalized anxiety,[53] as well as functional impairments[53,54] and social difficulties such as peer victimization.[55] Cross-sectional studies comparing symptomatology and clinical features between adults with early-onset of symptoms (in childhood or adolescence) vs. late-onset (in late adolescence or early adulthood) indicate more severe obsessions and compulsions[56,57] and higher co-occurrence of tic disorders[58,59] in early-onset OCD.

In terms of neurocircuitry, neuroimaging studies in children have reported alterations in activity of the CSTC circuits, such as dorsal prefrontal hypoactivation during OCD symptom provocation,[60] that are similar to those found in adult OCD.[9,10] Yet, there also appear to be differences in CSTC activation patterns between children and adults, with children showing amygdala hypoactivity[60] in contrast to the typically-observed hyperactivity of the amygdala in adults.[9,10] Cross-sectional studies including child and adult participants with OCD have reported some structural alterations that are shared between pediatric and adult OCD (thinner parietal cortex) and others that are specific to adult OCD (larger hippocampal and smaller pallidum volumes) or pediatric OCD (larger thalamic volumes).[61,62] Further, Busatto et al.[63] reported decreased regional neural activity in right thalamus, left ACC and bilateral inferior parietal cortex in adults who had first presented with OCD symptoms before age 10 years (early-onset OCD) compared to adults with late-onset OCD (first symptoms after age 12 years), suggesting different neurodevelopmental patterns of brain activation in these subgroups. These findings suggest that neurocircuit alterations in OCD may differ, at least in part, depending on the developmental course of the disorder.

However, to truly understand neurodevelopmental trajectories in OCD, longitudinal studies are needed and these are less common, especially in child and adolescent populations. Longitudinal studies examining changes in symptoms over time in children[64,65] and adults[66,67] have indicated that the types (or dimensions) of OCD symptoms experienced by patients remain remarkably stable over time, with between-dimension shifts being relatively rare (i.e., shift from symmetry/ordering to responsibility for harm symptom dimensions),[64,66,67] even as the specific symptoms within a dimension do frequently change.[65,68]

Studies investigating longitudinal alterations in neurocircuitry in relation to OCD and OCD-relevant constructs are difficult to conduct and have been relatively rare, yet the small number of studies that are available have identified developmental changes in areas of fronto-striatal circuitry, particularly in prefrontal regions. In a study of typically developing adolescents and young adults, Ziegler et al.[69] found that greater self-reported compulsivity at 14 to 24 years of age was related to reduced myelin-related growth over an approximately 1-year period in dorsolateral and dorsomedial frontal cortices (including ACC) and ventral striatum, aligning with a cingulate-striatal loop previously associated with OCD in neurocircuit models (Table 1). While observational (non-intervention) studies identify localized areas of brain volume decreases during development in OCD, a study looking at volume changes related to CBT found increases in medial orbitofrontal cortex (OFC) gray matter volume in response to CBT, with a further increase present in a subsequent 2 year follow-up period.[70] Interestingly, this increase of OFC volume was found only among younger OCD patients (those who were 8-12 years at baseline), but not older OCD youth (13-19 years) or typically developing control youth (who showed a decrease in OFC volume in both younger and older age groups), suggesting that CBT may alter the trajectory of brain structure in OCD only if administered at a young age.

Future work should aim to investigate whether the neurocircuit dysfunctions proposed in the models are present at or even before the onset of OCD, for example in children with subclinical obsessive-compulsive symptoms, and whether developmental changes of these circuits relate to changes in symptoms over time and the transition from subclinical to clinical levels of OCD symptomatology. Subclinical obsessive-compulsive symptoms in children are associated with elevated co-occurring symptoms of mood, anxiety, and psychotic disorders[71] and functional impairments similar to those seen in children who meet diagnostic criteria for OCD.[53] Further, large-scale population-based longitudinal studies show that subclinical OCD symptoms increase in severity with age,[71] and that the severity of subclinical symptoms in mid-to-late childhood (6-12 years) significantly predicts the severity of symptoms in late-childhood to adolescence (age 9-17 years).[72]

Concerning neurocircuitry, a recent study reported decreased functional connectivity between putamen/thalamus and limbic, sensorimotor and insula regions associated with subclinical obsessions and compulsions, ordering and doubting, respectively, in children without OCD or other neurodevelopmental or psychiatric conditions.[73] A large, population-based study also reported significant associations between subclinical obsessive-compulsive symptoms and increased functional connectivity of the sensorimotor circuit and decreased connectivity of the insula in children and adolescents,[74] consistent with the involvement of these circuits in OCD.[9,10] A recent study of brain volumes in a population sample of 2,551 children found significantly enlarged thalamic volumes in children with elevated obsessive-compulsive symptoms, but without an OCD diagnosis compared to children with low levels of obsessive-compulsive traits,[75] similar to findings in

children with an OCD diagnosis.[62] These findings suggest that some neurocircuit dysfunctions are likely present before the emergence of clinically significant symptoms, which may pave the way for early interventions.

Limitations related to etiological factors involved in OCD

Neurocircuit models of OCD do not consider the contribution of genetic and environmental etiological factors, or their interaction, to neurocircuit alterations. In terms of genetic factors, twin and family studies have shown that OCD is heritable, with elevated rates of OCD in first-degree family members of OCD patients.[76-78] Twin studies indicate that this heritability largely reflects shared genetic rather than shared environmental factors.[76] Further, neuroimaging studies report shared neurocircuit dysfunctions in OCD patients and their unaffected siblings, including hyperactivity of the pre-supplementary motor area during response inhibition[79] and hyperactive error monitoring functions of the ACC,[80] which may reflect neuro-endophenotypes of OCD, i.e., neurobiological markers of genetic risk for the disorder.

Considering molecular genetics findings, large-scale genome wide association studies (GWAS) have demonstrated that brain structure[81] and functional connectivity[82] are highly heritable. Meta-analyses of GWAS have revealed that single nucleotide polymorphisms (SNPs) associated with increased risk for OCD significantly overlap with SNPs associated with increased putamen and nucleus accumbens (NAcc) volumes[83] and that genes associated with OCD and compulsivity significantly overlap with genes expressed in the ACC, NAcc, and amygdala.[84] These findings suggest that common genetic variants may underlie dysfunctions in several of the neurocircuits proposed in models of OCD (Table 1) (see also Saraiva et al.[78]). Yet, the functional impact and clinical translation of these genetic variants continue to be a challenge mainly due to the non-coding nature of the majority of these variants and their pleiotropic effects.[85] Further, although gene expression follows a homogenous pattern across brain regions, it is highly dependent on cell type and neurodevelopmental stage.[86,87] Thus, early neurodevelopmental stages are likely to influence adult neuroanatomical structures and behavioral phenotypes, which further emphasizes the need for longitudinal studies investigating neuro-circuit dysfunctions, and the contribution of genetic factors, across development in OCD.

In terms of environmental factors, childhood trauma is associated with a diagnosis[88] and a less favorable clinical course (i.e., persistently severe symptoms over time)[89] of OCD in adulthood. The presence of childhood trauma has also been shown to predict atypical structure of brain regions included in neurocircuit models of OCD such as the orbitofrontal gyrus.[90] Furthermore, several studies have revealed gene x environment interactions, with the presence of alterations in genes involved in serotonin and dopamine signaling[91] and neurodevelopmental processes such as synaptic plasticity[92] increasing the elevated susceptibility to OCD associated with childhood trauma.

Immune disorders that cause inflammation have also been associated with OCD.[93] Inflammation is recognized to play a crucial role in atypical brain development[94] and neuroimaging work has found elevated inflammatory markers within CSTC circuitry in adults with OCD.[95] Together, these findings highlight the complexity of factors that contribute to the presence and severity of OCD symptoms and underlying neurocircuit dysfunctions. These factors may also affect treatment approaches. For instance, while childhood trauma was shown not to adversely affect treatment-related reduction of OCD symptoms,[96] it has been associated with co-occurring mood, eating and substance use disorders and suicidality,[97,98] which may complicate treatment choice and/or efficacy in OCD.[99,100] Augmentation of standard pharmacological treatment (SSRI) with anti-inflammatory agents has been shown to improve treatment response in OCD,[100-102] suggesting that inflammation may be an important treatment target for the disorder.

Limitations related to treatment methods

The effects of treatments such as CBT and SSRIs on neurocircuit function need to be better understood, as do those of more novel treatments (e.g., fMRI neurofeedback, rTMS) that are proposed to have more specific modulatory actions on neurocircuit and neurocognitive functions. For instance, regarding the more traditional OCD treatments (CBT and SSRIs), CBT has been shown to engage fronto-limbic and dorsal cognitive circuits involved in fear and emotion regulation,[11,12] which led us to propose that this treatment may be most effective for OCD patients with clinical profiles associated with those two neurocircuits[10] (Table 1). However, recent studies investigating effects of CBT on whole-brain structural and functional connectivity in OCD have reported widespread changes in several networks beyond the CSTC and fronto-limbic circuits, as well as changes in the interactions between different functional networks.[103,104] Similarly, based on neuroimaging and neurocognitive studies investigating fear and reward mechanisms in OCD, we proposed that SSRIs may be particularly appropriate for patients with fronto-limbic and ventral affective circuit dysfunctions[10] (Table 1). However, several neuroimaging studies have revealed brain-wide effects of SSRIs, with changes in several functional neural networks both following a course of treatment in OCD[105] and following acute administration in non-psychiatric volunteers.[106] Widespread alterations in brain structure have also been found in medicated compared to unmedicated individuals with OCD.[107] These findings indicate that CBT and SSRIs are likely to affect a range of neural and cognitive mechanisms. Further work testing the effects of these treatments on a variety of neurocognitive processes will be required to clarify for which clinical profiles and underlying neurocircuit dysfunctions these treatments are most appropriate.

Furthermore, in our neurocircuit-based taxonomy to guide OCD treatment,[10] we proposed that stimulation of the dlPFC using rTMS may be an effective treatment approach for OCD patients with the dysregulated fear profile (Table 1). Specifically, we suggested that dlPFC

rTMS could restore activity in the hypo-functioning dorsal cognitive circuit, thereby reinstating top-down control of dysregulated fear responses mediated by hyperactive fronto-limbic circuitry. In support, studies have shown improved functional connectivity between dorsal prefrontal and fronto-limbic regions following dlPFC rTMS in patients with OCD[108] and mood disorders.[109] However, a recent study using concurrent rTMS+fMRI to investigate brain-wide effects of dlPFC rTMS in patients with depression revealed activity changes in a range of regions throughout the frontal lobe as well as in primary somatosensory cortex, subgenual ACC, superior parietal lobe and temporal regions.[110] Importantly, the activation in each of these regions varied considerably across participants, with no two patients showing the same pattern of activation across areas.[110]

Similarly, while Eshel et al.[109] reported significant increases in functional connectivity between dlPFC and fronto-limbic regions following 4 weeks of rTMS stimulation of the dlPFC in depressed patients, they also found rTMS-related increases in global dlPFC connectivity, i.e., significant increases in connectivity between the targeted dlPFC region and all other voxels in the brain. These findings indicate that dlPFC rTMS has broad effects on regional neural activity and functional connectivity, rather than the neurocircuit-specific effects suggested in neurocircuit models. Further, the findings of Vink et al.[108] demonstrate that there is considerable inter-individual variability in the effects of dlPFC stimulation on other brain regions and neurocircuits, suggesting that not all patients may benefit from this treatment in the same way. There are also some barriers to clinical implementation of rTMS. For instance, it is unclear what the most effective stimulation protocols are for OCD in terms of the frequency of stimulation, target, number of pulses per session, number of sessions, and state dependency, and whether the optimal stimulation protocol should be personalized based on individual clinical or brain characteristics. Although TMS passes through skin, bone, and fat without resistance, there is a decline in intensity of the stimulation from the center of the coil, which reduces the focality of the stimulation and complicates the targeting of specific regions and neurocircuits.[111]

A final limitation of a neurocircuit-based approach to treatment for OCD concerns the process of selecting an appropriate "specific" treatment based on an individual patient's clinical or neurobiological profile. Important questions that arise here include whether the patient would be required to complete a neurocognitive test battery, MRI scan, or MEG/EEG recording before treatment is selected; if so, are these measures sufficiently sensitive to detect individual-level impairments and what "cutoff scores" would be used given that most of these tests do not have normative data indicating levels of impairment? Would a new "diagnostic manual" for the clinical profiles and neurobiological alterations that could occur in OCD be needed and is this feasible? Finally, could this type of assessment work for under-funded public mental health systems? This latter question is crucial, especially in the context of psychiatric care for individuals in low- and middle-income countries (LMICs) where the majority of

individuals with mental health problems may not receive treatment.[112] In some LMICs, particularly in Africa and India, there is one psychiatrist for every 100,000 people.[113] Access to psychiatric care is poor with long waiting times even in high-income countries.[112] It is difficult to imagine how a multi-method assessment that includes expensive neuroimaging scans and neuromodulatory treatments could be incorporated into general practice in psychiatry. These practical questions must be addressed for neurocircuit models to be clinically useful.

Future directions: advancing neurocircuit models of OCD and bridging the gap to treatment

Based on the limitations of current neurocircuit models of OCD discussed in this review, we highlight several avenues for further research in this area. A multi-method approach is needed to clarify the clinical profiles and underlying neurobiological mechanisms involved in OCD. Studies should include systematic assessments of the content of patients' subjective experiences of symptoms to identify clinical profiles and the extent to which such profiles co-occur in the same patients. Multi-modal neuroimaging techniques (fMRI, MRI, EEG/MEG) and carefully selected experimental tasks which engage the different neurocognitive functions implicated in the clinical profiles of OCD (fear regulation, sensory phenomena, habit-formation, response inhibition, reward processing, executive function) should be employed to more thoroughly characterize the neurobiological mechanisms that are associated with different and clinical profiles and their co-occurrence.

The combined use of different neuroimaging techniques may also help to address issues concerning the lack of specificity of experimental tasks in measuring particular neurocognitive processes. For example, the high temporal resolution of EEG means that neural activity can be broken down into short (tens of milliseconds) "components," which are robustly associated with discrete neurocognitive processes, e.g., in the go/nogo task a component referred to as the "N2" reflects conflict monitoring and a later component, the "P3," reflects inhibition.[18,19,114] This information can be combined with high spatial resolution data from simultaneously-recorded fMRI to localize the neurocircuits associated with each neurocognitive component.[115] Together, these data would give a clearer picture of the neural networks involved in the task and how they are altered in OCD. A handful of studies have used simultaneous EEG-fMRI in OCD (e.g., Grützmann et al.[116]), but the vast majority of research cited in support of neurocircuit models of the disorder has employed neuroimaging techniques independently. Repeated neuroimaging assessments in the same individuals should also be conducted to determine the reliability of neurobiological alterations linked to clinical profiles. In addition, several strategies could be used to address the low test-retest reliability of experimental neuroimaging tasks in eliciting patterns of brain activation. Previous work has shown improved reliability of task-based fMRI measures when they are computed from longer and repeated

scanning sessions[117] and when they are combined with other metrics, such as resting-state fMRI, in multivariate analyses[118] (for a full discussion, see Elliott et al.[21]).

Analytical approaches that are capable of integrating information from multiple assessments and neuroimaging techniques and relating that information to clinical profiles are also required. Predictive modelling based on machine learning pattern recognition algorithms will be an important tool in this regard. This method seeks to find the best predictive model of an outcome, e.g., a clinical profile, based on all available information, which can include neuropsychological task performance and structural and functional brain activity measured at different levels.[119] Importantly, predictive modelling avoids issues with multiple comparisons and low statistical power that arise when comparing multivariate data between clinical groups.[119] Indeed, a handful of recent large-scale studies have conducted data-driven analyses using machine-learning algorithms to investigate subtypes of OCD based on resting-state functional connectivity patterns and the extent to which those data-driven subtypes differ in treatment response to CBT,[120] and to investigate homogeneous subgroups of children with OCD, autism, or ADHD based on integrated measures of brain structure and clinical symptomatology.[121,122] These studies indicate that it is possible to identify subgroups within OCD and also across traditional diagnostic categories that are characterized by different neural alterations associated with different clinical profiles[121,122] or reductions in OCD symptoms in response to treatment with CBT.[120] A similar analytical approach is planned for the latest phase of our cross-site global study of OCD; we will apply machine learning methods to "multi-modal fusion" data (i.e., combined clinical, neuropsychological, and structural and functional neuroimaging data) to identify brain signatures of OCD.[123] Such data-driven approaches will be important for testing the subgroups of OCD related to underlying neurocircuit dysfunctions proposed in neurocircuit models.

While large-scale studies using the aforementioned multi-method approach and analytic techniques are needed to confirm the presence of clinical profiles and underlying neurocognitive dysfunctions in the OCD population, so too are n=1 designs with multiple measurements over different experimental conditions to investigate whether neurocognitive task performance and neural activity patterns are reliably linked with clinical profiles at the level of the individual patient. Recent work has indicated that some neural activity patterns are reliably measurable at the individual participant level in non-psychiatric volunteers,[124,125] although this analytical approach is still in its infancy. Most research in OCD has focused on group-level differences in brain structure and function and the feasibility of individual-level analyses will need to be evaluated in this population.

In addition, there is an urgent need for longitudinal studies to track stability and changes in clinical profiles and neurobiological alterations over time in OCD patients, under the influence of typical development, life events, and treatments. The effects of genetic and environmental factors as well as co-occurring conditions must also be investigated in these studies. Particular focus should be given to how these variables influence the presence of different clinical profiles and neurocognitive mechanisms and their waxing and waning course in OCD. Data on genetic, environmental, and developmental factors could also be incorporated in predictive modelling of clinical profiles of OCD along with neuropsychological and neuroimaging data. One example of this longitudinal design is the Brazilian High-Risk Cohort study (BHRC),[126] which follows a population sample of children over several years and collects repeated measurements of clinical symptoms, including OCD symptoms, neuroimaging, and genetic and environmental data. The Generation R study in the Netherlands is of the same longitudinal design.[75] Population-based studies in children such as these are particularly important since they provide the opportunity to study neural alterations that occur before the onset of clinically significant symptoms of OCD. These studies therefore allow inferences to be made about whether neural alterations are involved in the causal pathway to OCD symptoms, in contrast to cross-sectional studies of individuals with OCD in which neural alterations reported could reflect consequences of OCD symptoms and or epiphenomenal effects.

Steps needed to bridge the gap to clinical translation of neurocircuit models include further empirical studies investigating the effects of the treatment approaches proposed in the models on the neural and cognitive functions suggested to be associated with each clinical profile. Analyses testing whether OCD patients with particular clinical profiles (e.g., dysregulated fear or sensory phenomena) respond best to treatments that are suggested to target neurocircuit alterations underlying those profiles (e.g., CBT, SSRIs, dlPFC rTMS, and amygdala fMRI-neurofeedback for dysregulated fear; habit-reversal therapy, insula, and supplementary motor area neuromodulation for sensory phenomena) are also necessary. This should include n=1 designs assessing individual patients' responses to different treatments, separated by wash-out phases, as well as group-level analyses of treatment response in patients who share the same clinical profile. Crucially, research is needed to assess the most effective method, such as predictive modelling, of identifying individual patients with a particular clinical profile, associated neurocognitive alteration and neurocircuit dysfunction.

Finally, given the highly interactive nature of neurocircuits and the evidence that neurobiological alterations in OCD are not limited to changes in discrete neurocircuits, an effective approach to treatment may be to target key brain regions that act as connectivity "hubs" for several neurocircuits. Hub regions are cortical or subcortical areas that are characterized by a high degree of structural or functional connectivity (i.e., number of connections) with many other brain regions.[127] As such, hub regions are crucial for the integration of neural activity across distributed brain areas and efficient neural communication.[127] In individuals without psychiatric conditions, hub regions have been consistently found in parts of the anterior, middle, and posterior cingulate, OFC, dlPFC, caudate, inferior parietal lobe, cuneus, insula, supplementary motor area, and somatosensory cortex.[128-132] Neuroimaging studies have reported selective disturbances in hub regions

in OCD, with significantly higher degree of connectivity in the ACC, medial OFC, sensorimotor cortex, putamen, and cuneus hubs and significantly lower degree of connectivity in the inferior OFC, insula, and posterior cingulate hubs in OCD patients compared to non-psychiatric controls.[130,132] Increased degree of connectivity in two hub regions, the medial OFC and putamen, was also found to correlate with OCD symptom severity.[130,132] Treatments for OCD may therefore be optimized by targeting hub regions, which in turn may restore altered functional connectivity in several connected neural networks.

Conclusions

The burden of OCD on the lives of patients and their families, as well as the limited effectiveness of current treatments in about half of patients, motivates research on new treatments. The current approach of conducting randomized controlled trials (RCTs) that test the efficacy of treatments in reducing the severity of obsessions and compulsions in groups of patients with OCD, but with heterogeneous symptom profiles, has led to first-line treatments that can help up to 50% of patients. In the search for more effective treatments for individuals that do not respond sufficiently to first-line treatments, new strategies are necessary. Neurocircuit models of OCD have provided an important bridge towards this goal by linking aspects of the clinical phenomenology of OCD symptoms (clinical profiles) to specific neurocognitive alterations and underlying neurocircuit dysfunctions, which could be targeted in treatment. The most recent model[10] has also proposed specific treatment approaches for the different clinical profiles and neurocircuit dysfunctions in OCD, thereby creating testable hypotheses for a neurocircuit-based taxonomy for the treatment of OCD.

The present review highlights the limitations of current neurocircuit models and the challenges that should be addressed in further research in this area. These include complexities in brain and cognitive function and their assessment with experimental tasks, and the importance of considering a wider range of neurobiological mechanisms and neuroimaging techniques and etiological factors that may contribute to neurobiological alterations in OCD. The fact that clinical profiles, and consequently their underlying neurocircuit dysfunctions, co-occur in the same individual at the same time, change across development, and are frequently accompanied by co-occurring psychiatric conditions, further complicates the current interpretation of the scientific literature. Finally, current treatments do not preferentially target a specific neurocircuit, and instead affect several different brain areas. To address these limitations, we recommend several avenues for future research, including a multi-method approach to clarify the clinical profiles and underlying neurobiological mechanisms involved in OCD, data-driven analytical approaches, and a greater focus on individual-level analyses. Bearing in mind their limitations and considering contemporary knowledge of brain functions, current and future neurocircuit models in OCD will be useful in providing new treatment hypotheses to be tested to improve the lives of OCD patients and their families.

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