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Developing a Neuromodulation Tool to Suppress Intrusive Thinking

Things We (Think We) Know and Things We Need to Figure Out

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Abstract

Intrusive thinking is a core feature in multiple psychiatric diseases, including obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), substance use disorder (SUD), and Tourette syndrome. These diseases are not only bound by intrusive thinking, they also share similar disruptions in the functional architecture of the brain, including frontal-striatal-thalamic circuitry which is involved in salience attribution and shifting attention. As more is learned about the neural circuit dysfunctions involved in the initiation, maintenance, and attention to intrusive thoughts, it may become possible to develop noninvasive neuromodulation approaches to attenuate the presence of these thoughts or the morbidity associated with their existence in individuals. This chapter focuses on transcranial magnetic stimulation (TMS) as a tool to induce causal change in behavior, cortical excitability, and frontal-striatal activity. An overview is provided of the cortical and subcortical areas that are often implicated in intrusive thinking, using examples from Tourette syndrome, OCD, PTSD, and SUD. The hypotheses presented can be generalized past TMS to other invasive and noninvasive forms of neuromodulation. In conclusion, key questions are posed to move the field forward.

Introduction

As discussed in the other chapters of this book, there are many operational definitions for intrusive thoughts. While it is difficult to unify these definitions into one common framework, a familiar theme is present in all of them:

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a persistent, stereotyped mental pattern that aversively interrupts the flow of competing mental processes despite attempts to inhibit and/or counter these thoughts. One particularly compelling example is that intrusive thoughts are like a mental "tic" wherein, as in the case of Tourette syndrome, an individual may be able to suppress intrusive thoughts for some period of time, but eventually that cognitive buffer is broken down and the intrusive thought pattern floods the neural systems that kept it in check.

The clinical disorder that is most easily characterized as an impairment of intrusive thinking is obsessive-compulsive disorder (OCD), wherein recurrent thoughts or urges lead to debilitating levels of anxiety, distress, and resultant compulsive actions that patients typically fail to willfully suppress. The anxiety and distress associated with intrusive, unwanted thoughts are also a hallmark of posttraumatic stress disorder (PTSD). Similarly, intrusive thoughts about avoiding opiate or alcohol withdrawal or having time to "take the edge off" with a smoking break, fuel the growth of substance use disorder (SUD) and impair the ability for treatment-seekers to remain abstinent.

All four of these psychiatric conditions (Tourette syndrome, OCD, PTSD, and SUD) have intrusive thoughts at their core, yet existing behavioral and pharmacological treatment strategies for these diseases are very different. Modern psychiatry has only recently begun to approach disease treatment in a manner that focuses on core transdiagnostic symptoms of psychiatric disease rather than discrete disease labels. Inasmuch as intrusive thinking is a core symptom common to these disorders, it is certainly a research domain worthy of focus for treatment development.

In addition, these four diseases have something else in common: they all entail disruptions in frontal-striatal circuitry involved in limbic drive and cognitive control. Through recent advances in dosing and coil design, it appears that a noninvasive brain stimulation technique known as transcranial magnetic stimulation (TMS), approved by the U.S. Food and Drug Administration (FDA) to treat depression and OCD, may be a promising tool to target the functional neurocircuit substrates of intrusive thinking in these patients. TMS is one of several noninvasive techniques that can be used to modulate neural circuitry (see Figure 16.1). Here we introduce TMS as a tool to induce causal change in behavior, cortical excitability, and frontal-striatal activity. We provide an overview of the cortical and subcortical areas that are often implicated in intrusive thinking (using examples from Tourette, OCD, PTSD, and SUD) and outline several key questions that should be addressed to move the field forward.

The Application of Transcranial Magnetic Stimulation to Diseases of Intrusive Thinking

TMS is a noninvasive brain stimulation technique that can induce changes in neural activity in the cortex and in monosynaptic afferent projections. When

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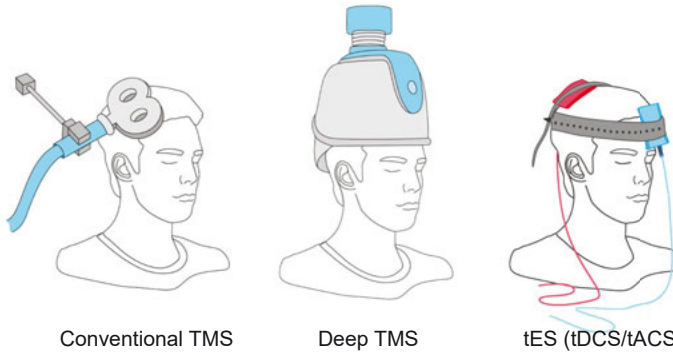

Figure 16.1 Noninvasive neuromodulation techniques used in individuals with psychiatric disorders that involve intrusive thoughts. The most common technique is the conventional transcranial magnetic stimulation (TMS), which is done by placing a figure-of-eight coil over a specific cortical location. This technique has been used to modulate craving in substance use disorder, impulse control in Tourette syndrome, obsessions in obsessive-compulsive disorder (OCD), and general symptoms of post-traumatic stress disorder. A unique form of TMS, known as "deep TMS," uses similar technology to modulate a wider, deeper area of cortex. This technique was approved for treatment of OCD in 2018. Transcranial electrical stimulation (tES) includes transcranial direct current (tDCS) and alternating current (tACS) approaches and has been used in these disorders as well, although there is still not clear evidence of its clinical efficacy. Reprinted with permission from Ekhtiari et al. (2019).

delivered repetitively (e.g., 600–3000 pulses every 40 seconds to 20 minutes), TMS can change cortical excitability and various behavioral phenomena for 30 minutes to several hours. When these repetitive sessions are given sequentially over a series of days (e.g., 10–30 sessions over 2–6 weeks), there may be lasting changes in functional connectivity in the brain as well as behavioral symptom resolution for several months to a year.

TMS was approved by the FDA as a treatment for major depressive disorders in 2008, and there are now TMS clinics in all 50 states in the United States, throughout Europe, Asia, Australia, and South America as well as a few new clinics in Africa. While the majority of the research in TMS has focused on optimizing treatment protocols for depression, there has been an exponential growth in the application of TMS to investigate and modulate these networks in populations with Tourette syndrome, OCD, PTSD, and SUD. The data has been growing fast, such that in 2018 the FDA approved a unique form of TMS to treat OCD. There is already approval for its use as a tool in SUD and OCD in Europe.

In developing a noninvasive neuromodulation solution for intrusive thinking, however, many questions remain:

- Is there a common neural circuitry that drives intrusive thinking across disease states? If so, can we use the same stimulation protocol for everyone or will there be biotypes that should be considered?

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- Assuming that we focus on TMS (as it is the only FDA-approved, noninvasive neurostimulation technique), what is the best cortical location and frequency?
- What is the best way to combine neurostimulation with pharmacotherapy and behavioral therapy to attenuate intrusive thoughts? Should these techniques be given simultaneously or in serial?
- Should we be pursuing closed-loop neuromodulation strategies for intrusive thinking (rather than current open-loop approaches)? Can we do that noninvasively?
- What stage of intrusive thinking is the optimal target for remediating intrusive thinking? Should the focus be on *prevention* (i.e., prevent the initiation or exacerbation of intrusive thoughts), *inhibition* (i.e., suppress intrusive thoughts), *reframing* (i.e., change the valence of a positive/negative thought), or *distraction* (i.e., enable a patient to shift attention away from the thoughts)?

Below, we will attempt to provide some insight into these questions. As a basis for this discussion, we begin with a review of several key principles that are important to understand, in terms of the capabilities and restrictions of current-generation TMS devices.

What Is Transcranial Magnetic Stimulation?

TMS can modulate neural excitability. It is a noninvasive form of brain stimulation that induces a depolarization of neurons through electromagnetic induction. Although a comprehensive review of studies that have demonstrated the principles of TMS is beyond the scope of this chapter, prior behavioral, electrophysiological, and neuroimaging work in this area is well described and summarized in several review articles (Fitzgerald and Daskalakis 2008; Hoogendam et al. 2010). The majority of our knowledge regarding the basic electrophysiological effects of TMS on the brain are from studies in the motor system. When applied over the hand knob of the primary motor cortex, a single, transient pulse of current through the TMS coil induces a reliable contraction of the contralateral hand, proportional to the amplitude of the induced electrical field (Barker et al. 1986). The amplitude of this motor-evoked potential (MEP) in the contralateral hand can be manipulated by pharmaceutical agents that effect voltage-gated sodium channels and glutamate (Ziemann and Rothwell 2000; Di Lazzaro et al. 2008). There is a dose-response relationship between the amplitude of the TMS pulse and the amplitude of the MEP. This dose-response relationship is referred to as the "recruitment curve" in brain stimulation literature and can be used as a measure of cortical excitability.

TMS can modulate neural pharmacology. Although hundreds of studies have evaluated the effects of various repetitive TMS protocols on behavior and

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cortical excitability (via EEG and functional MRI), very little is known about the effects of rTMS on neuropharmacology. The most cited studies in this domain have been done using positron emission tomography (PET) imaging, wherein the radioligand is given to the participant and then the TMS stimulation is delivered before the participant goes into the PET scanner. Using PET imaging, Strafella et al. (2001) have demonstrated that dorsolateral prefrontal cortex (dlPFC) stimulation leads to an increase in dopamine binding in the caudate. They also showed that when 10 rTMS is delivered to the left primary motor cortex, increases in dopamine are seen in the ipsilateral, left putamen. Using magnetic resonance spectroscopy, several studies have demonstrated the effects of TMS on cortical γ-aminobutyric acid (GABA) and glutamate (Stagg et al. 2009; Vidal-Pineiro et al. 2015; Iwabuchi et al. 2017). One of the most cited studies, by Stagg et al (2009), demonstrated that the attenuating effects of inhibitory, continuous theta burst stimulation (cTBS) on cortical excitability are related to an increase in GABA at the area of stimulation rather than a change in glutamate. Recently, Iwabuchi et al. (2017) showed that a single session of excitatory, intermittent theta burst stimulation (iTBS) to the dlPFC leads to a decrease in the GABA/glutamate ratio in both the dlPFC and in the insula, suggesting that it is possible to modulate paralimbic cortex through superficial PFC stimulation.

The following principles need to be considered as TMS therapeutic strategies are developed to address intrusive thinking.

Principle 1: Stimulation Depth

With a growing number of TMS coil designs, the depth at which stimulation should occur has become increasingly complex. The focality of TMS is related to the shape of the coil. There is a substantial body of literature devoted to computational modeling of electric field distributions associated with different coil shapes. In one of the most comprehensive papers, Deng et al. (2013) investigated the focality and penetration depth of 50 existing TMS coils. Their computational models revealed that typical figure-of-eight coil designs affected approximately 10 cm^2 of cortical surface, circular coils affected approximately 50 cm^2, and H-coil designs affected approximately 100 cm^2. Most flat figure-of-eight and circular coil designs had penetration depths of 1–2 cm^2, whereas the H-coil designs had consistently higher depths of 2–3 cm^2. A single TMS pulse from a standard figure-of-eight coil stimulates a 12.5 cm^2 area, which is approximately 1/125 (0.8%) of the cortical surface area. By comparison, deep brain stimulation can be at least an order of magnitude more precise than the most focal TMS coils available, with stimulation volumes ranging from 1–20 cm, depending on the electrode configuration (Wei and Grill 2005). Electroconvulsive therapy, on the other hand, appears to effect 94% of the brain and magnetic seizure therapy effects 21% of the brain (Lee et al. 2016). To put the focality of TMS in context with something that is meaningful to the

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average curious member of the public, 1/125th of the cortical surface is roughly analogous to the surface area of India (or half of Australia) relative to Earth (Hanlon 2017).

Principle 2: Polysynaptic Transmission

Beyond the direct cortical effects of TMS, it is possible to modulate monosynaptic (and possibly polysynaptic) targets of these cortical areas (Figure 16.2). The indirect effects of cortical TMS on monosynaptic afferent targets can be demonstrated through a behavioral assessment of the recruitment curve. When TMS is applied to the hand area of the primary motor cortex there is a dose-dependent change in the MEP of the hand contralateral to the TMS coil. This pathway from the motor cortex to the hand requires at least two neurons: the upper motor neuron, which originates in the motor cortex and terminates in the spinal cord, and the lower motor neuron, which originates in the spinal cord and terminates in the muscles that will contract to produce the MEP. The majority of upper motor neurons, however, terminate on interneurons, which then facilitate lower motor neuron activity. This suggests that TMS can have polysynaptic effects.

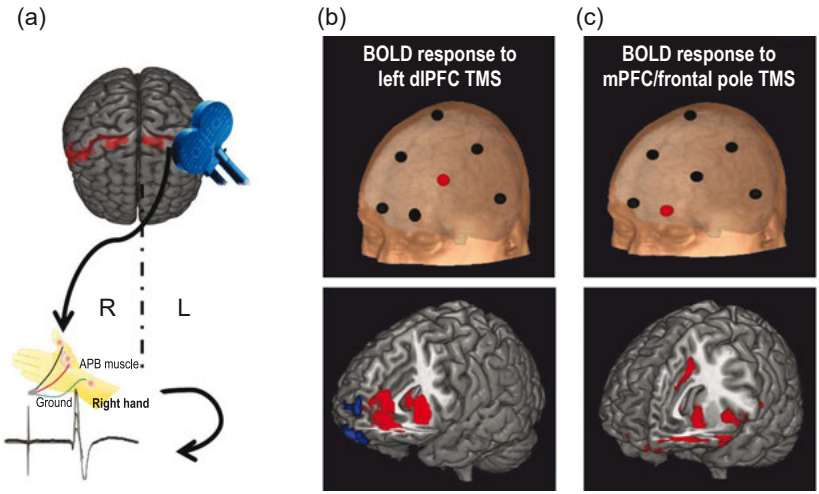

Figure 16.2 Polysynaptic effects: (a) Single pulses of TMS delivered to the hand knob of the primary motor cortex are able to transmit information down the cortical spinal tract, which crosses the synapse in the ventral horn, leading to contraction of the efferent target muscle in the hand, measured with motor-evoked potentials. (b) This polysynaptic engagement can be demonstrated in the cortex as well, wherein single pulses of TMS delivered to the left dorsolateral prefrontal cortex (dlPFC) lead to elevated BOLD signal in the dorsal striatum and ventral cingulate, whereas (c) TMS to the left frontal pole leads to BOLD signal in the ventral striatum, dorsal cingulate, and anterior insula. Adapted after Hanlon (2017).

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Principle 3: Frequency-Dependent Modulation

As stated above, when single pulses of TMS are delivered in rapid succession (rTMS), it is possible to change cortical excitability and various behavioral phenomena for a relatively brief period of time (e.g., 30 minutes to several hours; see Figure 16.3). These effects appear to be frequency dependent: low-frequency, continuous stimulation decreases cortical excitability whereas high-frequency, intermittent stimulation leads to an increase in cortical excitability (reviewed in Fitzgerald et al. 2006; Thickbroom 2007).

One of the first studies in this field was conducted by Pascual-Leone et al. (1994), who discovered that 20 pulses at 10 Hz and 20 Hz stimulation over the motor cortex produced an increase in the amplitude of the MEP, suggesting this frequency increases cortical excitability. Chen et al. (1997) then demonstrated that 15 minutes of 0.9 Hz TMS stimulation (810 pulses) to the motor cortex would decrease motor cortex excitability. In a sample of 14 individuals, 1 Hz TMS to the motor cortex for 15 minutes decreased the MEP by 20% for at least 15 minutes after stimulation. These data are compatible with preclinical electrophysiology studies which have demonstrated that 1 Hz stimulation induces long-term depression of neural activity in slice preparations of the motor cortex, visual cortex, and hippocampus.

While 10 Hz and 1 Hz TMS are still widely used, a unique bursting frequency known as *human theta burst stimulation* (TBS) has now gained significant traction in the field. Human TBS was first evaluated by Huang et al. (2005). Leveraging data from preclinical literature, which demonstrated that

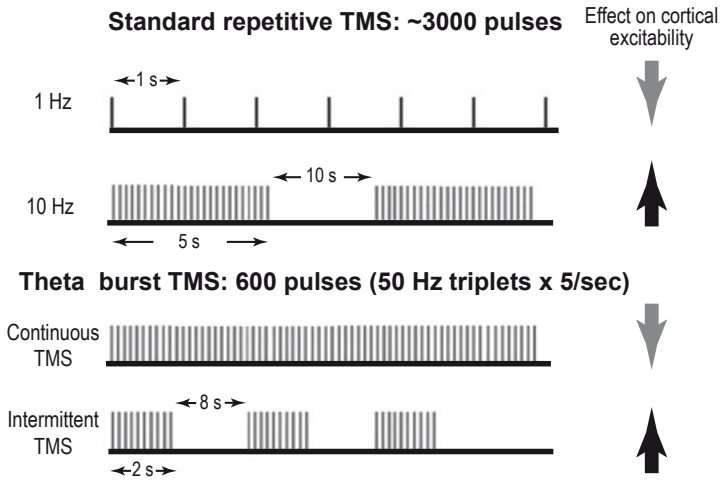

Figure 16.3 Frequency-dependent effects: When delivered in a repetitive manner, a single session can effect cortical excitability for 30–60 minutes.

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electrical stimulation of cortical slices in 100 Hz bursts five times per second (known as theta burst) can induce long-term plasticity (Bear and Malenka 1994; Malenka and Bear 2004), Huang et al. performed a clinical TMS study wherein TMS pulses were delivered to the motor cortex in 50 Hz bursts five times per second (human TBS). When TBS was delivered continuously for 600 total pulses, it decreased motor cortex excitability. When TBS was delivered in an intermittent pattern (2 sec on, 8 sec off) for 600 pulses, excitability increased. The effect sizes of these brief continuous TBS (40 sec) and intermittent TBS (190 sec) paradigms are comparable to studies of 1 Hz and 10 Hz. However, many publications have recently shown that there is high interindividual variability in TBS response, which has led to some caution in the reliance on this stimulation protocol (Vernet et al. 2014; Jannati et al. 2017).

Principle 4: Priming and State-Dependent Effects

A large body of literature demonstrates that the effects of TMS on behavior are brain-state dependent and may be amplified by priming the brain with either a behavioral task or brain stimulation (Opie and Cirillo 2017). One of the earliest studies in this field was by Iyer et al. (2003), who demonstrated that the attenuation of cortical activity with 1 Hz TMS can be amplified by priming the motor cortex with 6 Hz TMS. This was expanded to studies in the motor system and visual system, which demonstrated that there were brain-state dependent effects of TMS on cortical excitability (Silvanto et al. 2007, 2008a, b). Additionally, priming the brain with continuous TBS may enhance efficacy of intermittent TBS (Opie et al. 2017).

Although this body of research existed in sensory and motor control literature, it has only recently been harnessed by the clinical TMS research field. Whereas the recent FDA approval of TMS for OCD requires a behavioral prime, for example, neither the brain state nor the behavioral state of the individual was accounted for during the initial multicenter clinical trials of TMS for depression. This represents a latent opportunity for us to improve outcomes and minimize some of the interindividual variability that is observed in patients receiving clinical TMS treatment.

Within the addiction literature, a large clinical trial demonstrated that exposing a smoker to smoking cues (behavioral prime) before TMS amplified the effects of TMS on smoking cessation (Dinur-Klein et al. 2014). In this prospective, double-blind, sham-controlled study, 115 regular cigarette smokers were randomized to receive ten daily treatments of TMS. Immediately before each session, half of the participants were presented with visual smoking cues: cigarette consumption and nicotine dependence were reduced, and the effects were greatest in individuals that were exposed to smoking cues. In PTSD treatment, priming a trauma memory at the outset of each rTMS session has also been shown to enhance TMS effect sizes (Isserles et al. 2013). In this study, thirty PTSD patients were randomized to one of three groups: sham rTMS,

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real rTMS following exposure to a 30-second patient-tailored trauma script, or real rTMS following exposure to a 30-second patient-tailored neutral script. Participants received 12 sessions of real or sham rTMS (three sessions per week for four weeks, deep TMS H-coil). The only group with a significant improvement in the Clinician-Administered PTSD Scale was the group that received exposure to trauma scripts before each rTMS treatment.

The aforementioned studies all demonstrate that a priming stimulus amplifies the effects of a form of TMS intended to increase excitability in targeted networks. Although the mechanism through which cue exposure enhances the behavioral effects of rTMS are not clear, one possibility is that cue exposure reactivates latent memory traces, frequently referred to as an engram (Vernet et al. 2014), enabling them to be manipulated and reconsolidated (Opie et al. 2017). If this were true, priming may also be effective for TMS paradigms designed to decrease cortical excitability (e.g., 1Hz, cTBS). A recent study by our group demonstrated that, on average, individuals with cocaine use disorder, who were exposed to cocaine cues before and after continuous TBS, had a decrease in cocaine-cue reactivity following 3600 pulses of real but not sham TBS (Malenka and Bear 2004). Secondary analyses of the data, however, demonstrated that real cTBS decreased cue reactivity in individuals with a high baseline brain response to cues, whereas it increased cue reactivity in individuals with a low baseline brain response to cues. This bidirectional shift was not present following sham cTBS. While all individuals in this study received a behavioral prime (drug cue exposure), it seems that a behavioral prime was not alone sufficient. The directionality of TBS-induced effects was dependent on the baseline level of brain activity (neural state) in the TBS target; in this study (Malenka and Bear 2004), the medial PFC.

Potential Neural Circuit Targets for Neuromodulation of Intrusive Thinking

One of the key advances in the neuroimaging literature over the last twenty years is that brain regions organize their activity into coherent functional networks (Figure 16.4). Through functional magnetic resonance imaging (fMRI), these networks appear as correlations of the low-frequency fluctuations in BOLD signal between brain regions. Many networks were originally identified via data-driven methods from brain activity at rest, and are called *resting-state networks*. However, these networks reliably appear in ongoing brain activity during tasks, and meta-analyses of task-based activation also reveal consistent *functional networks* similar to those identified at rest.

Several functional networks have been studied extensively that have relevance to intrusive thinking: the default mode network (DMN), containing the medial PFC and posterior cingulate; the salience network (SN), containing the anterior cingulate and anterior insula; and the executive control network

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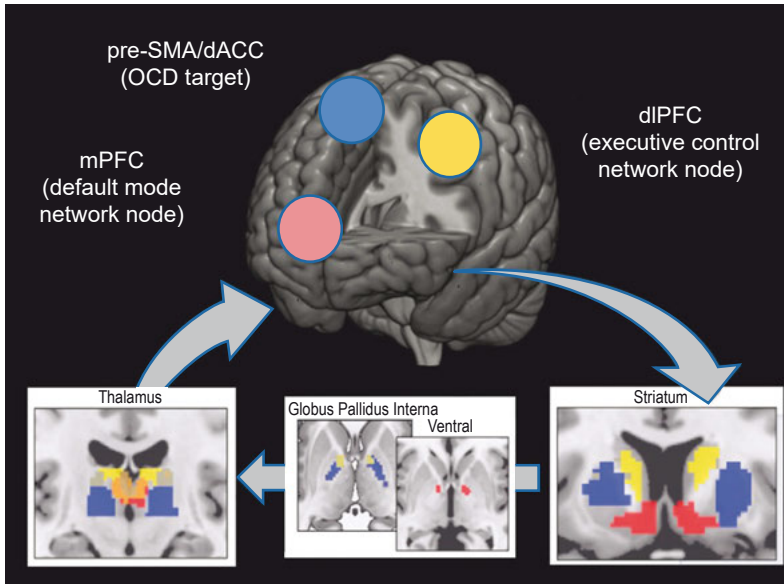

Figure 16.4 Candidate neural circuits amenable to modulation for intrusive thinking. Typically, therapeutic neuromodulation approaches require that a specific neural system be identified. The therapeutic strategy can then target the nodes of this neural system. This can be done invasively (e.g., through deep brain stimulation) or noninvasively (e.g., using TMS, transcranial electrical stimulation, pulsed ultrasound). Three cortical nodes may be putative targets for neuromodulation based on their role in intrusive thinking and their striatal-thalamic connectivity: the medial prefrontal cortex (mPFC, red), the left and right dorsolateral prefrontal cortex (dlPFC, yellow), and the presupplementary motor area (pre-SMA, blue). The striatal, pallidal, and thalamic nodes of these circuits are shown in the lower panels. Adapted after Morris et al. (2016).

(ECN), containing the dlPFC and posterior parietal cortex. DMN is the best known and most studied of these functional networks. It serves various introspective functions related to intrusive thinking, including mind wandering, recollection and prospection, rumination, and self-reflection. Other "task positive" networks act in opposition to the DMN. These networks activate during behaviorally regulated task performance and externally focused cognition. For example, the SN activates for transitions from introspection to task performance as well as during task initiation and switching. The ECN is involved in cognitive control, working memory, and in tasks governed by external stimuli, whereas functional connectivity in the DMN is typically high during tasks of internal monitoring. In this manner, the ECN and DMN are considered anticorrelated networks.

Etkin and colleagues demonstrated the central importance of the SN as a common neural substrate across psychiatric illness categories (Goodkind et al.

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2015). They performed a meta-analysis of structural abnormalities across six psychiatric disorder categories, including OCD, PTSD, and SUD, and found that all of them showed gray matter volume reductions in the dorsal anterior cingulate cortex and anterior insula. In a parallel meta-analysis of functional neurocircuit anomalies during cognitive processing tasks across psychiatric disorders, Etkin and colleagues demonstrated that the SN, in conjunction with the broader frontoparietal ECN, is hyporeactive among these patients during cognitive demands. Importantly, the ECN is recruited for cognitive regulation as well as emotional regulation, and the dlPFC target most frequently utilized in therapeutic rTMS is seated within this network. As such, the transdiagnostic effects of rTMS may, in part, be attributable to ECN upregulation and its influence on attenuating intrusive thinking and associated negative affect. In addition to putatively increasing activity of the ECN with rTMS, we might predict that intrusive thinking could alternatively be attenuated by either decreasing the activity of the DMN or enabling the SN to switch more effectively from the DMN to the ECN. These hypotheses have not been directly tested but are amenable to systematic evaluation through TMS.

Questions and Hypotheses

1. Using TMS (because it is the only FDA-approved noninvasive technique), what is the best cortical location and frequency?

Strategy 1 Decrease the amplitude of intrusive thoughts at rest by dampening the medial orbitofrontal cortex (OFC) connectivity (a node in the DMN). Several studies have demonstrated that individuals with OCD have elevated activity in medial aspects of the OFC. Three studies that targeted the OFC with TMS showed improvements in OCD symptoms. These were all relatively small studies that applied 1–3 weeks of treatment and showed changes that lasted up to one month.

Strategy 2 Increase control over intrusive thoughts by increasing dlPFC connectivity (a node of the ECN). The dlPFC is the FDA-approved target for the treatment of depression and has been investigated as a treatment target for PTSD, SUD, and OCD. The first study to explore the use of TMS for OCD demonstrated that a single session of 10 Hz TMS decreased compulsions but not obsessions, yet the effects lasted for eight hours (n = 12 individuals). Although these results were promising, they have been difficult to replicate. Two recent studies have demonstrated that several weeks of TMS may improve OCD, but again, the obsessive component does not seem to respond very well. This may be because the obsessive component relies more heavily on subcortical structures such as the basal ganglia and amygdala. While 10 Hz TMS to the left dlPFC and 1 Hz TMS to the right dlPFC have been evaluated

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as a target for PTSD, with mixed success, intrusive thinking is not often reported as a primary outcome measure. Consequently, with mixed results from the dlPFC, it is still unclear if targeting this area is likely to improve intrusive thoughts.

Strategy 3 Target the supplementary motor area/pre-SMA. The first studies that targeted the pre-SMA examined the use of TMS for patients with OCD and Tourette syndrome. At the end of treatment, patients showed general reduction in OCD symptoms, an improvement in functioning, and reductions in depression and anxiety. Importantly, the improvements held for at least three months. This study was followed by a second study with 21 OCD patients and a more careful study design. After four weeks of TMS treatment, patients showed notable decreases in OCD symptoms as well as a reduction in depression and anxiety; benefits were still present for most patients three months later.

Although TMS targeting the pre-SMA has been shown to be the most effective, it is not clear whether this is indeed the only or best area of the brain to target, as pre-SMA studies are the only ones thus far that use doses and treatment protocols similar to the standard of care for depression. These positive results are, however, very encouraging and are helping us move forward.

In 2018, a unique form of deep TMS was approved by the FDA to treat OCD. This type of TMS has a wider cortical field and likely modulates a large portion of the medial PFC and cingulate cortex, including the SMA/pre-SMA. Although it is not clear exactly which of these brain regions is responsible for the clinical effect (or if all are necessary), these data suggest that the dorsal medial wall of the PFC may be a good target for modulation. In an interim analysis of a larger study, the research team evaluated the effects of 10 Hz, 1 Hz, and sham TMS on OCD symptoms in 23 individuals (25 sessions over five weeks). They demonstrated that although there was no significant interaction between group and time with this sample size, the effect size was higher with 10 Hz TMS compared to 1 Hz TMS. Hence, the remainder of the participants were randomized to 10 Hz TMS or sham TMS for a total sample of 30, wherein 10 Hz led to a significant reduction in OCD symptoms up to one month after the five weeks of TMS (Carmi et al. 2018). These data led to an 11-site clinical trial of 42 individuals who received six sessions of daily TMS to this medial PFC target.

2. What is the best way to combine behavioral therapy (including mindfulness and neurofeedback) with TMS to maximally attenuate intrusive thoughts? Should this be given simultaneously or in serial?

As described earlier, there is growing evidence that the effects of TMS can be amplified by priming the individual (and perhaps pushing the brain into a specific state) before TMS is administered. One of the key components of the 2018 FDA approval of TMS for OCD was that TMS had to be given in the presence of a personalized visual cue that caused stress and anxiety for the patient (e.g., placing a purse on the dirty floor in front of someone with

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obsessional thoughts about dirt). It was assumed that this external cue places the brain in a primed state, which would then be modulated by the TMS.

Based on these empirical results from rTMS experiments and from a strong preclinical foundation regarding manipulation and reconsolidation of memories, it is likely that any neuromodulation approach for intrusive thinking should involve putting the individual in a state where the intrusive thoughts are present and perhaps bothersome.

3. Should we pursue closed-loop neuromodulation strategies for intrusive thinking (rather than current open-loop technologies)? Can we do this noninvasively?

Given that intrusive thoughts are frequently transient and share some of the same temporal properties of a seizure (e.g., largely unpredictable onset time but with some known triggers, an episodic disease feature rather than a stable state as is seen in mood disorders or chronic pain), a closed-loop system may be more effective and appropriate for intrusive thinking than an open-loop neuromodulation approach (Figure 16.5).

Open-loop neuromodulation typically refers to a device that provides a fixed stimulation protocol over a fixed period of time. Currently, most invasive and noninvasive neuromodulation approaches are open loop (e.g., TMS, DBS). It is easy to see the value of a closed-loop system, which could include "sensing technology" to detect changes in the brain state, and then dynamic stimulation settings, which could adjust to the individual patient's neural needs. Closed-loop stimulation technology has shown promise as a treatment for various diseases (Widge et al. 2017). The most successful closed-loop system in clinical trials thus far has been developed, FDA approved, and is now deployed for use in intractable epilepsy. The leads of this device (NeuroPace) are implanted into an epileptic focus in the brain. It monitors activity in the areas, can detect the prodrome of seizure activity, and when a seizure begins it will deliver stimulation to block the growth of that activity. This is referred to as responsive neurostimulation and received approval from the FDA in November, 2013. In the years since its approval, it has been successfully employed in hospitals throughout the United States: several trials demonstrated a 53% seizure reduction after two years and a 70% median seizure reduction after five years (Geller et al. 2017). Closed-loop stimulation has also been used in the spinal cord for pain management (the RestoreSensor™ System, Medtronic, Minneapolis, MN). Although no noninvasive, closed-loop brain stimulation devices have been approved for clinical use yet, there is extensive growth in this field (Bergmann et al. 2016).

There are also non-device-based closed-loop neuromodulation strategies. Simpler versions include a "human in the loop": clinicians observe the recorded brain signals and provide manual adjustment of the stimulation rather than the device automatically self-adjusting. Other techniques such as real-time

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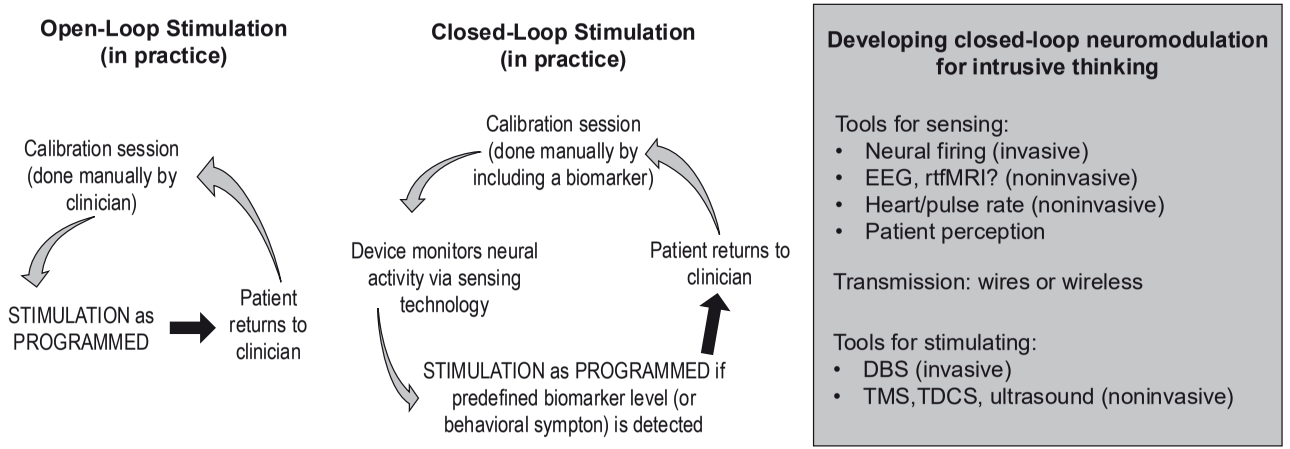

Figure 16.5 Open- and closed-loop neuromodulation options for intrusive thinking. Given the temporal profile of intrusive thinking, a closed-loop neuromodulation approach may be more beneficial—one that includes the ability to detect aberrant brain states (or behavioral states) and adapt its stimulation properties accordingly (e.g., turning itself on/off, modifying the frequency, changing the amplitude). A critical element involved in closed-loop technologies, however, is the reliability of the underlying biomarker it is trying to sense. In practice, standard "open-loop" techniques such as TMS and DBS are actually closed-loop systems, because the patient always returns to the clinician to have the parameters adjusted. New generation closed-loop techniques, however, may enable these adjustments to be made in real time, responding to endogenous neural changes and increasing the "agency" of patients by enabling them to modify the settings based on their own perceptions. This may be particularly useful for intrusive thinking.

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fMRI feedback, EEG feedback, and mindfulness strategies may also be useful approaches for intrusive thinking.

4. What is the best treatment strategy: *preventing the initiation* of intrusive thoughts or increasing the ability of the patient to *shift their attention away* from the thoughts?

When designing a neuromodulation approach for intrusive thoughts, the neural regions targeted and the dosing parameters used will likely be different if the goal is to help individuals shift their attention away from intrusive thoughts than if the goal is to stop them from happening. If the goal is to stop the initiation of intrusive thoughts, it is possible that targeting the DMN (perhaps using TMS directed at the medial PFC) might be a fruitful strategy. Alternately, if the goal is to enable individuals to shift their attention away from thoughts which target the salience network, a deep form of TMS directed at the cingulate or insula might be the best strategy, given its role in set-shifting and attributing value.

Conclusion

Intrusive thoughts are a common, transdiagnostically relevant feature of many psychiatric conditions including Tourette syndrome, SUD, PTSD, and OCD. With the approval of TMS as a tool to treat OCD in 2018, we are in the early stages of an era of rapid discovery regarding the use of neuromodulation to alter intrusive thoughts that plague these patient populations. Although several concepts of rTMS treatment are robust and replicable (e.g., regional specificity, depth of the magnetic field, dose-dependent amplification of behavior, polysynaptic engagement, frequency-dependent effects), many key components of TMS treatment development have not yet been widely explored, especially for intrusive thinking (e.g., optimal number of sessions per day or in total, the use of behavioral primes to amplify TMS treatment effects, the effects of applying TMS before vs. after behavioral therapy, the use of TMS to amplify pharmacotherapy treatment). As study of the neural circuitry that underlies the initiation, maintenance, and distraction from intrusive thinking matures, we will be better prepared to design biologically informed and rigorous neuromodulation clinical trials in this domain.

Here, we have attempted to introduce TMS as an innovative new tool which can modulate brain activity in a circuit-specific, frequency-dependent manner as well as to review current knowledge regarding the pharmacologic effects of TMS. While development of TMS as a new treatment tool is still in its infancy, we hope to have sparked interest in the need to develop a neural circuit-based treatment tool—one that is available to our patients—and to increase our knowledge of the synergy between pharmacotherapeutics and brain

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stimulation interventions. A large body of knowledge suggests that frontostriatal circuit activity is a significant biomarker involved in intrusive thinking. Through closed-loop brain stimulation techniques, it may be possible to develop an adaptive, personalized neural circuit-based treatment for patients.

It is important to note that lasting behavioral change may require more than just brain stimulation. Just as the plasticity potential of a primed neuron is higher than an unprimed neuron, TMS may have higher efficacy when an individual is engaged in the cognitive/emotional process they wish to amplify or attenuate. Hence, TMS is likely to be most effective when combined with a pharmacotherapeutic agent that lowers the threshold for cortical excitability or with behavioral interventions (e.g., exposure therapy or contingency management). Nonetheless, while these statements are based on preclinical literature and human learning theory, they await rigorous evaluation.

As the field continues to grow, we hope to see more interactions between clinical and preclinical neuroscience researchers from electrophysiological and pharmacological backgrounds. With any luck, through the continued refinement of open- and closed-loop brain stimulation tools, we may soon be rigorously evaluating noninvasive brain stimulation solutions for intrusive thinking. The quest for a sustainable treatment solution will undoubtedly require a complementary approach to modifying the pharmacology, neural circuitry, and ultimately the behavioral manifestations of intrusive thinking in these complementary cohorts of patients.

Acknowledgments

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