



A mathematical model of reward and executive circuitry in obsessive compulsive disorder



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ABSTRACT

The neuronal circuit that controls obsessive and compulsive behaviors involves a complex network of brain regions (some with known involvement in reward processing). Among these are cortical regions, the striatum and the thalamus (which compose the CSTC pathway), limbic areas such as the amygdala and the hippocampus, as well as dopamine pathways. Abnormal dynamic behavior in this brain network is a hallmark feature of patients with increased anxiety and motor activity, like the ones affected by OCD. There is currently no clear understanding of precisely what mechanisms generate these behaviors.

We attempt to investigate a collection of connectivity hypotheses of OCD by means of a computational model of the brain circuitry that governs reward and motion execution. Mathematically, we use methods from ordinary differential equations and continuous time dynamical systems. We use classical analytical methods as well as computational approaches to study phenomena in the phase plane (e.g., behavior of the system's solutions when given certain initial conditions) and in the parameter space (e.g., sensitive dependence of initial conditions).

We find that different obsessive-compulsive subtypes may correspond to different abnormalities in the network connectivity profiles. We suggest that it is a combination of parameters (connectivity strengths between regions), rather than the value of any one parameter taken independently, that provide the best basis for predicting behavior, and for understanding the heterogeneity of the illness.

1. Introduction

1.1. The obsessive-compulsive disorder and its brain dynamics

Obsessive-compulsive disorder (OCD) is a severe mental disturbance affecting around 2–3% of the US population. Its symptoms are chronic intrusive thoughts (obsessions) and/or repetitive behaviors (compulsions), which can lead to significant impairment in psychosocial functioning (American, 2000; Leonard et al., 1990). While medication plans and behavioral therapy may benefit some patients, 20–40% of OCD patients—often those most severely affected—remain refractory to treatment (Skoog and Skoog, 1999; Bourne et al., 2012).

According to the American Psychiatric Association, obsessions are repetitive, intrusive, and distressing thoughts, ideas, images, or urges that often are experienced as meaningless, inappropriate, and irrelevant, and persist despite efforts to suppress, resist, or ignore them (American, 2000). Compulsions are repetitive, stereotyped behaviors and/or mental acts that are used to diminish the anxiety and distress associated with the obsessions (American, 2000). It has been noticed that obsessions and compulsions are often linked by content. For

example, obsessive recurrent thoughts about erring may trigger compulsive checking of the work, and obsessive contamination concerns may lead to compulsive washing routines (Markarian et al., 2010). Although the DSM-IV criteria imply that it is possible for a person to experience compulsions without obsessions or vice versa, the vast majority of OCD patients have both obsessions and compulsions. Indeed, only 2.1% of patients with OCD report predominant obsessions, 1.7% report predominant compulsions, and more than 95% reported both obsessions and compulsions on the Yale-Brown Obsessive Compulsive Symptom Checklist (Foa and Kozak, 1995).

Structural and functional neuroimaging studies converge on evidence that abnormalities of obsessive compulsive behavior arise from abnormal neural activity in a wide network of cortical and subcortical areas. This network consists primarily of the orbitofrontal cortex (OFC) and the anterior cingulate cortex (ACC), the striatum (the ventral striatum in particular, also known as the nucleus accumbens – NAc), the thalamus and the amygdala (and other limbic regions), but also includes dopamine regulation from the ventral tegmental area (VTA) (Bourne et al., 2012; Menzies et al., 2008; Rotge et al., 2008, 2010; Haber and Brucker, 2008).

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The orbitofrontal cortex (OFC) is active in the regulation of emotional and fear responses, as well as in positive and negative valence processing (Kringelbach and Rolls, 2004). The OFC is also involved in behavioral planning and expected reward valuation. Dysfunctions of these processes are likely involved in the repetitive compulsions and driving obsessions of OCD, and may be represented by the altered OFC activity seen in this illness. Imaging (PET and fMRI) studies have shown increased activity in the OFC in OCD patients, both during resting state and with symptom provocation (Bourne et al., 2012).

The anterior cingulate cortex (ACC) plays a role in motivation and conflict monitoring, as well as in determining discrepancies between desired and anticipated state (Graybiel and Rauch, 2000). ACC has close connections to the motor cortex, and, together with the OFC, plays an important role in action selection subsequent to stimulus valuation. It has been suggested that altered activity in these two cortical areas contributes to dysfunctional signaling of conflict between the desired and the current state—that may lead to the repetitive actions (compulsions) characteristic of OCD (Bourne et al., 2012; Graybiel and Rauch, 2000).

The thalamus is often viewed as a hub of information, being tightly connected to a wide network of brain areas. It has multiple functions, including that of processing sensory information and relaying it to cortical areas, as well as that of “subcortical motor center” (Evarts and Thach, 1969). As part of the cortico-striato-thalamo-cortical circuit, the thalamus has been studied in OCD, with evidence showing increased activity in both resting state and with symptom provocation (McGuire et al., 1994).

The striatum (and more generally, the basal ganglia) has long been implicated (as part of the cortico-striato-thalamo-cortical loop) in the pathophysiology of obsessive-compulsive disorder and remains central to neurobiological models of OCD. The sensorimotor, associative, and limbic loci in the basal ganglia are widely implicated in motor, cognitive, and emotional aspects of behavior, respectively (Harrison et al., 2009). The ventral striatum in particular (nucleus accumbens) plays an important role in processing rewarding and reinforcing stimuli. In a study by Figeo et al. (2011), obsessive-compulsive patients showed attenuated reward anticipation activity in the nucleus accumbens compared with healthy control subjects, possibly leading to a decreased ability to make beneficial choices in expectation of a reward. The authors present these results in support of the conceptualization of OCD as a disorder of reward processing and behavioral addiction (Figeo et al., 2011).

Limbic regions are critically involved in the association of external stimuli with emotional value and the acquisition of conditioned fear responses. In OCD, abnormal activity in limbic structures may underlie the stimulus-triggered anxiety which often urges the patient to execute compulsions. While the amygdala and hippocampus have not received as much attention in the OCD literature as the areas of the CSTC loop, newer studies reveal their potentially critical contribution to the brain dynamics of the illness, and their potential implications to its treatment (e.g., through supporting hippocampal neurogenesis Bourne et al., 2012). Existing studies offer conflicting evidence on whether OCD patients present functional and structural limbic abnormalities when compared to healthy controls (Kwon et al., 2003; Busatto et al., 2000). These discrepancies may arise from the heterogeneity in the pathophysiology of OCD, depending on severity and type of obsessions/compulsions (Bourne et al., 2012). For example, a study using proton magnetic resonance spectroscopy (Besiroglu et al., 2011) reported amygdala and hippocampus abnormalities in patients with autogenous obsessions (i.e., that do not emerge in response to identifiable external stimuli), abnormalities which were not found in patients with reactive obsessions (evoked by specific external stimuli).

The ventral tegmental area (VTA) is known to play, via dopamine modulation, a critical role in motivation, reward-related behavior, attention, and multiple forms of memory (Malenka et al., 2009).

With its wide net of projections to a variety of fields, the activity of dopamine neurons confers motivational salience to the reward (via its connections with the nucleus accumbens), reevaluates it in light of new experiences (via the ties with the OFC), contributes to memory consolidation (via its ties with the hippocampus and amygdala), contributes to the reward-seeking motor control, to suppression of behaviors that compete with goal oriented actions and to control of attention (via its actions in the prefrontal cortex) (Malenka et al., 2009).

It is not surprising that some of these areas are known to be critical to the processing of rewards and to movement execution. New studies have been investigating the relationship between abnormalities in reward processing and the symptoms of OCD. It has been suggested that patients with OCD may develop dependency upon compulsive behaviors because of the rewarding effects following reduction of obsession-induced anxiety (Figeo et al., 2011). We investigate some of these possibilities in our modeling work.

The existing conflicts between results in the specialty literature suggest that OCD, like other mental illnesses, has a heterogeneous etiology, and that there may be multiple biophysical mechanisms underneath what is being addressed as a homogeneous disorder. Considering the heterogeneity of OCD may be most important when investigating regions only weakly implicated in OCD (such as the amygdala), but that may nonetheless significantly affect pathology (Bourne et al., 2012).

It is in this context that mathematical modeling can be successfully used in exploring potential mechanisms for different OCD subtypes. In this study, we aim to verify some of the current specific hypotheses that relate OCD symptoms to disruptions of connectivity and functional dynamics within the reward/executive network. While most imaging studies present these effects as separate possible causes or triggers of obsessive-compulsive behavior, we rather suggest that it is a complex combination of all these factors (and possibly other, unknown ones) which govern the behavior of the network. Our mathematical model presents the advantage of allowing us to analyze theoretically the effects of some of these factors taken separately, but also in combination. These effects predict different network dynamic regimes, which can then be compared with the dynamic patterns seen in imaging time series, and further, with behavioral dynamics observed in OCD patients.

Among the many neuroimaging studies of brain structure, activity and connectivity in OCD, up to date very few have been specifically designed to explore and understand *coupled dynamic patterns* of different brain areas in OCD patients. Based on what the existing literature suggests as potential important trends, we will consider, for this paper, a phenomenology of symptoms. While clinically speculative, these phenomena represent our mathematical interpretation of existing neuroimaging and behavioral results found in OCD. As a first step, in this paper we compare the modeling results against these “symptomatic” patterns, and we generate quantitative hypotheses, which can be further tested in conjunction with clinical data specifically collected for this purpose.

On one hand, the contribution of the amygdala to emotional arousal and fear extinction in general has been well supported in neuroimaging (Francisco Sotres-Bayon et al., 2004). As commented before, augmented amygdala involvement in OCD patients during symptom provocation might correlate to fear expression in OCD, linking it to other anxiety disorders. Two studies investigating this effect in multi-symptomatic, unmedicated patients documented amygdala hyperactivation across all OCD symptom dimensions as a common, anxiety-related neural response correlate. The studies found amygdala hyperactivation in patients both during passive viewing (Simon et al., 2010), as well as during self-referential processing of symptom-related pictures (Simon et al., 2014). This group difference corresponded to patients' subjective ratings of arousal, unpleasantness, and anxiety symptoms, but was independent from individual anxiety and depres-

sion scores. While not all imaging studies of OCD have identified consistent effects in the amygdala (Busatto et al., 2000; Saxena and Rauch, 2000), discrepancies may arise from variations in the pathophysiology of OCD depending on severity or subtype of obsessions (Bourne et al., 2012), or on the relationship between the nature of the obsessions and abnormal fear processing (Via et al., 2014). Broadly speaking, however, obsessive thoughts, via their effect on arousal and anxiety state, have the ability to produce a heightened limbic response—identified in our model as a high-amygdala state.

On the other hand, among the various functions that have been ascribed to the ACC are modulation of attention and executive function by influencing sensory and response selection (Bush et al., 2000). In particular, recent studies suggest that cells in the rostral cingulate motor area play a part in motor selection based on the amount of reward (Wenderoth et al., 2005). More precisely, such cells seem to be profoundly involved in processing information about assessing the reward obtained by executing a current movement and selecting the next movement if the reward is not satisfactory. Data suggest that anterior cingulate hyperactivity may affect selection, generation and control of self generated actions, and thus may explain the uncontrolled repeated activity characteristic to compulsive behavior. A PET study suggests that the observed reduction of metabolism in the cingulate cortex after treatment may just be an epiphenomenon resulting from the reduction of compulsive symptoms (Perani et al., 1995). Based on this evidence, we associate in our model anterior cingulate hyperactivity with the aberrant executive control found in compulsive episodes—and we identify it mathematically as a high-ACC state.

It is, however, the *interplay* between these regions' dynamics and plasticity that may be most representative of OCD symptoms. The ACC and the amygdala (together with their functional connections) consistently emerge from neuroimaging studies as brain regions crucially involved in fear learning and emotional processing (Toyoda et al., 2011), with the rostral ACC (mentioned above as one of the higher order motor areas in the cortex) also appearing as key to gating the efficiency of amygdala-dependent auditory fear conditioning learning (Bissière et al., 2008). In this paper, we will give particular attention to the possible dynamic interplay between these two areas, reflecting the cycle of emotional arousal. It may be the case that a patient with OCD symptoms may be in an “obsessive state” (characterized by high arousal and amygdala hyperactivation), in a “compulsive state” (characterized by stereotypical movement execution, with enhanced ACC activation, associated with distraction from the intrusive thoughts), or can be performing an oscillation between the two, in which tightly coupled amygdala-ACC dynamics allow for only a temporary alleviation of anxiety, after which the return of obsessions restarts the OCD cycle.

The fear-alleviating effect of compulsions has been studied in the literature in the more general form of distraction-induced amygdala downregulation (Simon et al., 2014). Distraction was characterized by stronger activation especially in attention areas including the dorsal ACC (Kanske et al., 2010). This may explain why some studies have related elevated anxiety caused by intrusive obsessive thoughts not only to aberrant amygdala function, but to hyperactivity in the ACC (Deckersbach et al., 2006). In fact, it may be the case that the activity in ACC actually increases not as a direct effect to obsessions, but rather when compulsions onset as a distraction coping mechanism aimed to damp obsession-triggered anxiety. The use of attentional distraction as coping behavior has been demonstrated to be an effective technique for managing clinically significant intrusive thoughts (Najmi et al., 2009). Patients' ability to distract themselves from intrusive thoughts, behaviors and accompanying elevated anxiety—and thus regulate amygdala hyperactivity—is essential for functioning in situations when compulsions cannot be performed (Simon et al., 2014). These results support the potential for a vicious obsessive-compulsive cycle, of escalating anxiety followed by calming movement execution, with the amygdala and ACC oscillating out of phase.

The presence of amygdala/ACC oscillations is additionally sup-

ported by fMRI studies of low-frequency fluctuations in OCD patients versus controls. The amplitudes of low-frequency fluctuations (ALFF) are popular measures for the magnitude of low-frequency oscillations in resting-state fMRI (*r*-fMRI) data. Both measures can be directly derived from the spectral power of *r*-fMRI time courses. Numerous studies suggest that ALFF might be usable as biomarkers for a variety of diseases including schizophrenia, major depressive disorder, and obsessive-compulsive disorder (Küblböck et al., 2014). In particular, patients with OCD presented increased ALFF in the bilateral OFC and ACC compared to normal controls, while ALFF in the amygdala were associated with emotional conflict resolution (Xue et al., 2016).

The rest of the paper is organized as follows: In Section 1.2, we describe the known projections within our network of interest. In Section 1.3, we list a few hypotheses that relate OCD clinical symptoms to connectivity and functional problems in this network. In Section 2, we introduce our mathematical model and discuss how these hypotheses are reflected in the construction. In Section 3, we analyze the effect on dynamics of changes to specific parameters of interest, considered separately and in combination. We focus on analyzing the transitions between different asymptotic regimes, as well as on relating the position and type of the attractors (equilibria and cycles, in this case) to long-term behavioral regimes found in OCD (e.g., oscillation between elevated amygdala due to anxiety, and elevated ACC when performing compulsive movement execution). Finally, in Section 4, we discuss some of the broader implications of our model, as well as limitations and further work.

1.2. The reward/executive network

Our circuit of interest is comprised of a few modules, whose coupled behavior governs the brain's emotional and cognitive responses to positive and negative rewards (see Fig. 1): the cortex, the limbic system, the basal ganglia, the thalamus and the dopamine system. Below, we describe the most important excitatory (glutamate) and inhibitory (GABA) pathways as well as the more subtle dopamine modulations delivered by the ventral tegmental area.

The main cortical areas implicated in this circuitry are the orbitofrontal cortex (OFC), and the anterior cingulate cortex (ACC). The *orbitofrontal cortex* receives glutamate (excitatory) projections from the thalamus (Bourne et al., 2012), as well as from limbic areas

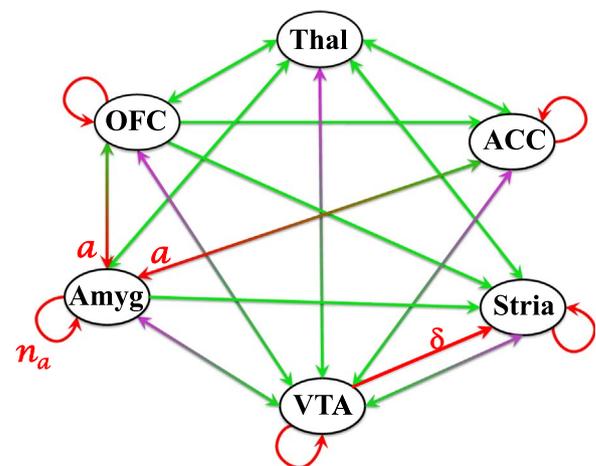


Fig. 1. Representation of our model brain circuit, with node dynamics representing activation levels in the orbitofrontal cortex (OFC), anterior cingulate cortex (ACC), thalamus (Thal), amygdala (Amyg), striatum (Stria) and ventral tegmental area (VTA). The synaptic pathways are represented by colored directional arrows, where green represents glutamatergic excitation, red represents GABA inhibition, and purple represents dopamine modulation. The key parameters used in our sensitivity analysis are marked above the corresponding arrows: b_1 , b_2 , a , n_a , δ . (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

such as the amygdala (which projects primarily to the lateral division of the OFC) and the hippocampus (which connects primarily with the medial OFC) (Francisco Sotres-Bayon et al., 2004; Elliott et al., 2000; Cavada et al., 2000). The *anterior cingulate cortex* also receives glutamate afferents from the thalamus (Gigg et al., 1992) and the medial OFC (Elliott et al., 2000), as well as from limbic areas (subiculum, a part of the hippocampus) through the mammillary tract.

The limbic system is known to have important contributions to the reward circuitry. The amygdala and the hippocampus have been identified in particular to be responsible for emotional modulation of reward processing. The *amygdala* is kept under inhibitory control both by the orbitofrontal cortex (NANCY L REMPEL-CLOWER, 2007) (provided primarily by lateral OFC (Elliott et al., 2000)), and by the ACC (Etkin et al., 2011; NANCY L REMPEL-CLOWER, 2007). This inhibition is provided to central and basal regions of the amygdala via indirect excitation of inhibitory (GABA) intercalated cells (ITC). The amygdala also receives glutamatergic input from other limbic areas (e.g., the hippocampus Kishi et al., 2006; Richter-Levin and Akirav, 2000) and from the thalamus (Bourne et al., 2012; Turner and Herkenham, 1991). The *hippocampus*, in turn, is connected via symmetric afferent and efferent pathways (Swenson, 2006) to the OFC (primarily to the medial parts (Elliott et al., 2000)), to the amygdala and to the thalamus.

The basal ganglia are part of the cortico-thalamo-striato-cortical loop of the reward circuit, which appears to be the most implicated in OCD abnormalities. The *striatum* is the central piece of the CTSC circuit, with its D1R- and D2R-medium spiny neurons (MSNs) receiving inputs (often not symmetric) from a wide variety of sources. Both D1R- and D2R- MSNs receive (via direct and indirect pathways, respectively) unbiased glutamate inputs from the thalamus and from the OFC (Wall et al., 2013), and also glutamate projections from the hippocampus (Liddle et al., 2000). In addition, the limbic (i.e., anterior cingulate) cortex sends glutamate inputs primarily to D1R-MSNs (Wall et al., 2013), while the motor cortices send a stronger glutamate proportion of inputs to D2R-MSNs (Wall et al., 2013). The amygdala also sends glutamate projections (Yager et al., 2015) to the ventral striatum (nucleus accumbens) (Cho et al., 2013), including to the striatal shell (Fudge et al., 2002, 2004), which expresses equally D1R- and D2R-MSNs (Yager et al., 2015).

The *globus pallidum internum* (Gpi) (Liddle et al., 2000) receives direct inhibitory inputs from D2R-MSNs, as well as indirect excitatory inputs from the D1R-MSNs (via a pathway of two inhibitory and one excitatory connections, with relay steps in the globus pallidus externum and in the subthalamic nucleus). The Gpi sends in turn glutamate inputs to the *thalamus* (Liddle et al., 2000), which also receives excitatory inputs from the OFC (Bourne et al., 2012), from the ACC, through the mammillary bodies (Bourne et al., 2012; Vogt and Gabriel, 1993), and from limbic regions: from the hippocampus, via mamillo-thalamic and hippocampothalamic pathways (Vogt and Gabriel, 1993), and from the amygdala (Bourne et al., 2012; Krettek and Price, 1977).

Dopamine modulation in the network. Dopamine neurons from the ventral tegmental area (VTA) innervate many areas including the ventral striatum (nucleus accumbens) (Liddle et al., 2000; Pan et al., 2010), olfactory bulb, amygdala, hippocampus, orbital and medial prefrontal cortex (Cetin et al., 2004), and the cingulate cortex. In turn, the VTA receives glutamate and GABA inputs from a wide net of areas (including cortical and limbic areas) (Russo and Nestler, 2013). Excitatory prefrontal projections to the VTA play an important role in regulating the activity of VTA neurons and the extracellular levels of dopamine (DA) within forebrain regions. Previous investigations have demonstrated that prefrontal terminals synapse on the dendrites of DA and non-DA neurons in the VTA (Carr and Sesack, 2000).

In addition to these well established effects of dopamine on reward processing, there are also a few newer findings which complete our knowledge of VTA connectivity, and which we incorporated in our model circuit. The dopamine projection to the thalamus was thought to

be non-existent, when a schizophrenia study found high levels of dopamine in the thalamus of patients with otherwise normal dopamine levels in striatal regions (Oke and Adams, 1987). Subsequent work showed that the dopamine projection to the thalamus is not negligible, and further studies incorporated aberrant thalamic dopamine, together with other hypotheses, into a systems model of psychosis (Moghaddam, 2010; Lisman et al., 2010).

Finally, there is new evidence that VTA dopamine neurons can also release glutamate or GABA, contributing to wider functional effects (Russo and Nestler, 2013). On one hand, dopaminergic neurons were shown to inhibit action potential firing in both direct- and indirect-pathway striatal projection neurons through release of GABA (Tritsch et al., 2012). On the other hand, a recently discovered population of glutamate neurons in the VTA projects to the nucleus accumbens (NAc), lateral habenula, ventral pallidum (VP), and amygdala (Hnasko et al., 2012).

1.3. Obsessive compulsive disorder and connectivity in the reward circuit

We will build our model upon these known aspects of neural circuitry. Clearly, the network implicated in reward processing and motion execution is very wide, and a comprehensive model of all its regulatory aspects would be undesirably complex, even when considered in isolation from external interactions, and at a single—region of interest—scale. With our model, we choose to focus in particular on a few aspects involved in the dynamics of OCD, and on trying to verify a set of specific hypotheses that have been stated in the current literature in relation to the neurobiological underpinnings of this illness.

A few studies support the broad hypothesis that OCD is associated with functional alterations of brain corticostriatal networks. These findings emphasize that functional connections in the network are modulated by affective and motivational states and further suggest that OCD patients may have modulation abnormalities in this network (Jung et al., 2013). A variety of studies have additionally related OCD symptoms to abnormal connectivity between cortico-striatal modules and the limbic and dopamine systems. This is not surprising, since the latter are responsible for crucial aspects of emotional responses and reward processing, suggesting their potential involvement in the anxiety control whose malfunction may lead to obsessive thoughts and compulsive movement execution. Below are the existing connectivity hypotheses that we consider in our model:

Hypothesis H1: Enhanced OFC projections to the NAc correlate with OCD symptoms. An fMRI study comparing 21 patients with OCD and 21 matched healthy controls (Harrison et al., 2009) found abnormal and heightened functional connectivity of ventrolimbic corticostriatal regions in patients with OCD. More precisely, patients with OCD had significantly increased functional connectivity along a ventral corticostriatal axis, implicating the orbitofrontal cortex and surrounding areas. The specific strength of connectivity between the ventral caudate/nucleus accumbens and the anterior orbitofrontal cortex predicted patients' overall symptom severity.

Hypothesis H2: Decreased amygdala connectivity with the NAc correlates with OCD symptoms. A few studies have confirmed the increased functional connectivity between the nucleus accumbens and the lateral orbitofrontal cortex during resting-state in OCD patients (Jung et al., 2013). A tractography study showed that in fact this functional abnormality reflects a structural issue: the fractional anisotropy of fibers between the orbitofrontal cortex and the striatum was higher in OCD patients compared to healthy controls (Nakamae et al., 2013). Additionally, patients were shown to have decreased connectivity between the nucleus accumbens and limbic areas such as the amygdala during incentive processing (Jung et al., 2013).

Hypothesis H3: Decreased VTA dopamine modulation of the NAc correlates with OCD symptoms. A new study by Harrison et al. (2009) found an unanticipated effect: patients with OCD showed evidence of

reduced functional connectivity of the ventral striatum with the ventral tegmental area (Harrison et al., 2009). In healthy controls, the VTA provides the ventral striatum (nucleus accumbens) with dense dopaminergic innervation that is presumed to be critical for cortically driven action selection and long-term plasticity of corticostriatal loops (Surmeier et al., 2007). While current evidence from in vivo studies suggests that striatal dopamine activity may be elevated in patients with OCD, findings have been mixed (Denys et al., 2003). In our model, we will test the implications of this hypothesis.

Hypothesis H4: Decreased inhibition of the amygdala increases anxiety. In our previous modeling work, we have studied two types of inhibition to the amygdala, in relation with their potential contributions to amygdala control: self-inhibition within the amygdala, and external inhibition from cortical areas (Rădulescu, 2008, 2009). Decreased inhibition of both types has been related to emotional disturbances such as anxiety and psychosis. We hypothesize that inhibition of the amygdala also plays an important role in the dynamics of OCD symptoms.

2. Model construction and hypotheses

We showed in the introduction that a very complex network of regions is involved in the abnormal reward and emotional processing. Out of a wide collection of potential mechanisms, we outlined a few distinct hypotheses of specific abnormalities potentially leading to the increased anxiety and motion executive drive which may feed into obsessive and compulsive behavior. To investigate these factors, we tailored our system to optimally address these specific problems. We included in our network the following coupled areas (see Fig. 1): O = orbitofrontal cortex, C = cingulate cortex, A = amygdala, T = thalamus, S = ventral striatum = nucleus accumbens, δ = dopamine/ventral tegmental area. These are the areas which our focus hypotheses hold responsible for the network dynamic abnormalities found in OCD. This will help keep the system simple enough to be computationally tractable, while still sufficiently comprehensive to illustrate our set of hypotheses. Some extensions and future work are discussed in Section 4.

To fix our ideas mathematically, we decided to introduce all non-dopaminergic connections as their first (linear) Taylor approximation term around zero. The dopaminergic connections were introduced as nonlinear (sigmoidal) terms, since the nonlinearity may better capture in this case the diffuse effect and the timing of dopamine at its target sites.

$$\begin{aligned} dO/dt &= -nO + mA + mT + f_\mu(O, \delta) \\ dC/dt &= mO - nC + mT + f_\mu(C, \delta) \\ dA/dt &= -aO - aC - n_A A + mT + m\delta + f_\mu(A, \delta) \\ dT/dt &= mO + mC + mA - nT + mS + f_\mu(T, \delta) + 1 \\ dS/dt &= b_1O + b_2A + mT - nS - m\delta + f_\lambda(S, \delta) \\ d\delta/dt &= m(O + C + A + T + S) - n\delta \end{aligned} \quad (1)$$

The signs of the linear coefficients in the system are based on the type of synaptic pathway between the respective interconnected regions—excitatory (glutamatergic) or inhibitory (GABA-ergic)—as described and referenced in Section 1.2.

While there are a few known techniques of computing relative strengths of inter-regional connectivity from imaging time series (Friston et al., 2003; Sun et al., 2004; Rogers et al., 2007), there are at this time very few quantitative imaging studies addressing connectivity abnormalities in OCD. A recent study by Schlösser et al. (2010) used dynamics causal modeling to derive and compare fronto-cingulate effective connectivity in 21 OCD patients versus 21 matched controls. Another study by Stern et al. (2012) quantified and examined the altered interactions at rest between fronto-parietal and default mode networks (including posterior cingulate cortex, medial frontal cortex, posterior inferior parietal lobule, and parahippocampus) in 30

patients with OCD versus 32 control subjects. Neither of these, however, estimates the whole collection of connectivity coefficients necessary to verify all of our hypotheses. Therefore, for the purpose of this study, the magnitudes of our parameters were not obtained empirically, but rather motivated theoretically. Future imaging work is aimed at computing specifically the parameters needed for future iterates of this model.

We used fine tuning of the parameters to initially place the system in a range of dynamic functioning that reproduces phenomenologically “normal” behavior, as discussed in Section 1.1. We then used qualitative reasoning to study the behavior of the system under small perturbations of the key parameters: increasing the magnitude of a parameter reflects strengthening of the coupling between the two corresponding regions; decreasing the magnitude represents weakening this coupling. When analyzing the dependence of dynamics on the strength of these connections, we will start by observing the system while varying one parameter at the time, and we will search for the points where the dynamics exhibit transitions between qualitatively different regimes (e.g., transformation of a stable equilibrium into an attracting cycle). We will then investigate how these transitions change when perturbing two key parameters simultaneously.

The parameter m represents the strength of excitatory control throughout the network; n is the level of self-damping (taken to be uniform for all areas in the network), so that, in the absence of all outside stimuli, activity in an isolated area would die out. While clearly the values of n and m are in reality different in each node and respectively between node-pairs, this is a simplification aimed to help with tractability when performing a parameter sensitivity analysis of the system. A too high-dimensional parameter space would make this task practically impossible. This is a typical modeling negotiation between realism and approachability.

The coefficients b_1 and b_2 are, respectively, the level of orbitofrontal excitatory control of the striatum and the level of amygdalar excitatory control on the striatum. To illustrate these effects in our model and verify hypotheses H1 and H2, we allowed them to vary within a range of values around what we considered the baseline ($m=1$). One of our goals will be to perform a sensitivity/bifurcation analysis of the model with respect to these two parameters, and verify whether the systemic dynamic effects of increasing b_1 and decreasing b_2 are consistent with those described in the empirical literature.

The far reaching, complex dopamine modulation on all areas in the network was represented by the sigmoidal function

$$f_\mu(X, \delta) = \frac{1}{e^{-\mu(X-\delta)} + 1} - \frac{1}{2}$$

This nonlinearly increasing function reflects a plausible biological modulation, with a slow take-off at low dopamine levels, and a window of high-sensitivity followed by saturation. Since it has been suggested that dopamine modulation can have both excitatory and inhibitory effects, we allow both positive and negative values for the function f_μ , determined by the level of activation \times already existent in the target area. The highest sensitivity (position and slope at the inflection point) is tuned by the parameter μ , so that higher μ values can be interpreted as a stronger dopamine effect. The baseline level for this parameter was considered to be $\mu = 0.1$ in all simulations. In order to test hypothesis H3, we allowed the effect of dopamine on the nucleus accumbens (and the corresponding sensitivity parameter λ) to be varied independently from the dopamine contributions to the other areas.

In order to test Hypothesis H4, we allowed to test for different levels of amygdalar inhibition. The coefficient n_A , representing the strength of self-inhibition within the amygdala, was allowed to vary around the baseline value $n_A = n$. The coefficient a , representing the strength of the cortical inhibition of amygdala (assumed to be identical from the orbitofrontal and the cingulate cortices), was allowed to vary in a range around the baseline $a=2$.

3. Results

A linear analysis of the system suggested bifurcation points with respect to some of our key parameters. This included pairs of conjugate imaginary eigenvalues at specific parameter states, opening the potential for Hopf bifurcations, and for the subsequent transitions into and out of cycling behavior. We then used numerical methods to analyze the nonlinear system and investigate our specific hypotheses.

Exploring hypotheses H1 and H2: We have investigated the effects on the system's steady state when changing the values of the parameters b_1 and b_2 , and observed that, as hypothesized, both effects (also in combination) are associated with typical obsessive-compulsive symptoms, as predicted by our model.

For a normal range of (b_1, b_2) values, the system has an attracting spiral, so that, in absence of outside stimulation, activation in all areas of the network decays to a baseline level, to which we will refer as the “control baseline.” The value of the control baseline is intrinsically meaningless, and will be only used to interpret, by comparison, the behavior in other parameter regimes (which may deliver a higher or a lower baseline than the control level, or an oscillation around it).

When the parameter b_2 is increased, the attracting spiral evolves (through a Hopf bifurcation) into a cycle. This cycle represents a long-term sustained high/low oscillation in the network's activity. In particular, the amygdala and the cingulate cortex oscillate out of phase, so that the network alternates periods of elevated amygdala (high anxiety) with periods of elevated cingulate (high compulsion for motor execution). We will call this an *obsessive/compulsive cycle*. Our numerical computations found the Lyapunov coefficient at the Hopf bifurcation to be very close to zero (of the order of 10^{-16}), meaning that the transition is for all practical purposes a critical Hopf bifurcation. Subsequently, the cycles born from this bifurcation are non-isolated, neutral cycles. That is: in the post-bifurcation, cycling regime, different initial conditions lead asymptotically to different cycles, suggesting that symptom severity and temporal evolution (e.g., amplitude and duty cycle) may depend on the original state of the system (possibly affected by certain environmental factors).

When the parameter b_1 is increased, the system evolves towards a steady state with progressively lower amygdala and higher thalamo-cortical activity. In particular, the cingulate levels increase with b_1 . We call this regime *compulsive release*, since one may interpret the increased drive for repeated motor execution as anxiety alleviating.

While the individual effects of b_1 and b_2 seem relatively clear, the effect on dynamics of these two factors in combination is not trivial to interpret. For small values of b_1 (top row in Fig. 2), decreasing b_2 does not seem to have dramatic consequences, only changing the speed of convergence to the stable equilibrium. For larger b_1 , however (second and third rows in the same figure), decreasing b_2 may transition the system from a range of obsessive/compulsive oscillation to a range of compulsive release. From a different perspective: for larger b_2 values (right panel column in Fig. 2), increasing b_1 pushes the system from a controlled regime into a wide obsessive/compulsive cycle. For smaller values of b_2 (left two panel columns in the same figure), increasing b_1 pushes the system from a control regime to increased compulsion release.

Exploring hypothesis H3: We studied how the behavior described above is altered when changing the dopamine modulation on the nucleus accumbens. We have studied this by increasing the sensitivity λ of the sigmoidal modulation used to model the dopamine impact specifically on the variable S : for a higher λ , the sensitivity interval begins at lower activity levels of S , allowing dopamine to have a higher impact on this area. This increase dims the effects observed at lower dopamine modulation. In Fig. 3, the equivalent of Fig. 2 for higher dopamine sensitivity of the NAc, one can notice similar—but milder—effects and transitions when increasing and respectively decreasing b_1 and b_2 .

Exploring hypothesis H4: In previous work, we suggested that

amygdalar self-inhibition is an important factor providing stability to the dynamics of the emotion regulatory network (Rădulescu, 2008, 2009). Here, we again observed the effect of increasing the amygdalar self-inhibition n_A , for different connectivity profiles (b_1, b_2) . We noticed that, for low values of b_1 and high values of b_2 (corresponding, based on our previous considerations, to a well-controlled system), a slight increase in n_A will only allow trajectories to converge faster, but not much affect the position of the stable equilibrium (Fig. 4, left panel). We observed more substantial effects, however, if the system is already operating in an OCD-prone regime, with a large b_1 or/and a low b_2 . For high b_1 and high b_2 , increasing n_A brings the system from a range in which the trajectories converge to a stable cycle—back through a Hopf bifurcation to a regime of relatively fast convergence to a stable equilibrium, at relatively low activation levels of A and C (Fig. 4, center panel). For high b_1 and low b_2 , increasing n_A results in a decrease in the asymptotic amygdala levels, at the expense of increasing cortical activation (less anxiety, but more pronounced compulsion, Fig. 4, right panel).

The bifurcation diagram in Fig. 5 illustrates the Hopf curve dividing the cycling regime (below the curve) from convergence to a stable equilibrium (above the curve), and how the position of this curve changes when changing the value of n_A . The left panel shows, in the (b_1, b_2) parameter plane, that a lower n_A triggers this transition at lower values of b_2 . The right panel shows that higher n_A only leads to slightly higher C levels at the transition into the stable equilibrium regime.

We also studied the effect of increasing the cortical inhibition of the amygdala, represented in our model by the connectivity strength a between orbitofrontal/cingulate areas and the amygdala. While one would expect a stronger inhibition of an area to result in lower activation levels in that respective area, the actual effect produced by the coupling in the network was rather counterintuitive: it was the levels of cortical activation that were in fact reduced as an effect of increasing amygdalar inhibition. In the case of a well controlled network (small b_1 and large b_2), lower cingulate activation (shown in Fig. 6, left panel) resulted without any detriment to amygdalar function. However, in the case of a larger b_1 and/or a lower b_2 , arousal levels actually increased by increasing a , either as an increase of the amygdala steady state (Fig. 6, right panel), or as an oscillation with increased amplitude in the amygdala component (Fig. 6, center panel).

The bifurcation diagram in Fig. 7 illustrates how the Hopf curves between cycling and convergence to a stable equilibrium depend on the value of a . The left panel shows, in the (b_1, b_2) parameter plane, that a lower a triggers this transition at higher values of b_2 only in a range of low b_1 , and that the effect is swapped for higher b_1 . The right panel shows that lower a leads to significantly higher C levels at the transition into the stable equilibrium regime, and that this effect is exacerbated in the high b_1 and low b_2 range.

4. Discussion

In this study, we illustrated how a mathematical model of connectivity in a brain network can be used to study the phenomenology of OCD. We focused primarily on investigating how specific connectivity hypotheses of OCD reflect on behavioral dynamics, as per our modeling setup. We found that different known abnormalities of the reward/executive network affect differently the network dynamics, predicting different types of behavioral regimes associated with OCD. Here, we would like to discuss our analytical findings and put them in the broader perspective of their meaning and relevance to the study of OCD.

Based on its known activation during emotional arousal, we interpret high amygdala as high level of arousal/anxiety associated with the obsessive aspect of the OCD symptomatology. Based on its crucial role in initiating movement execution, we interpret high cingulate cortex activation as the elevated executive drive that in our case relates to the compulsive aspect of the OCD symptomatology. The

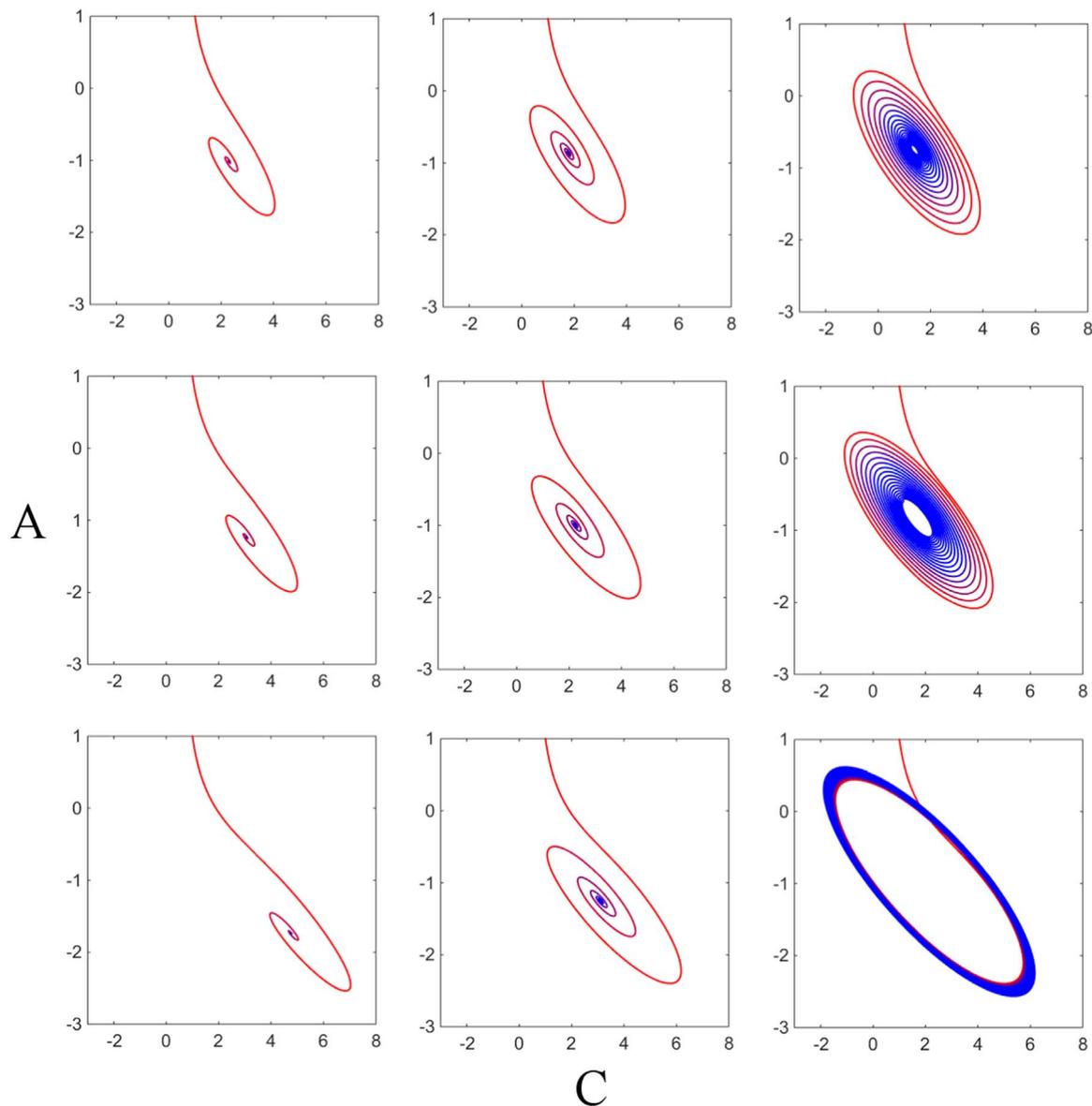


Fig. 2. Attracting states of the system for different values of the connectivities b_1 and b_2 . All panels show the evolution of a typical trajectory in a (C,A) slice (i.e., activation in the amygdala on the vertical axis versus activation in the cingulate cortex on the horizontal axis). The simulations were produced for $\lambda = 0.1$ (representing lower dopamine modulation of the NAc). Each row shows a different b_1 value: $b_1=0.4$ (top); $b_1=0.8$ (middle); $b_1=1.2$ (bottom). Each column shows a different b_2 value: $b_2=0.4$ (left); $b_2=0.8$ (center); $b_2=1.2$ (right). Other parameter values: $m=1$, $n=1.4$, $a=2$, $\mu = 0.1$.

different regimes that we identified in our network reflect these behavioral characteristics.

Qualitatively speaking, one can distinguish between three types of possible asymptotic regimes. A first potential steady state is characterized by low amygdala and high cingulate activations. A plausible behavioral interpretation is that, in such a regime, the compulsive movement execution redirects to some extent the obsessive thoughts, and diffuses the anxiety. In more lay terms, the compulsion execution is calming. Second, there is the counterpart regime in which the obsessive thoughts build up into a high anxiety (high amygdala) state, with no release coming from movement execution (low cingulate). A third regime is an oscillation between these two ends (prevalent in OCD [Foa and Kozak, 1995](#)), with obsessive periods followed by compulsive periods, with their duration and severity (duty cycle), depending itself on the specific hardwiring (parameters) of the system. We interpret our results in light of these three asymptotic regimes.

We showed that increased orbitofrontal–nucleus accumbens (OFC–NAc) connectivity leads, as hypothesized, to more pronounced OCD features. The precise type and strength of this relationship additionally

depend on the ranges of other parameters. For example, if in conjunction with a high amygdala–striatal (A–NAc) connectivity, increasingly higher values of OFC–NAc will push the system into gradually wider oscillations between obsessive and compulsive periods. In conjunction with a low A–NAc, increasingly higher values of OFC–NAc will drive the system towards a preferentially compulsive state. These findings are generally in agreement with both hypotheses $H1$ and $H2$, although they also suggest that the dependence on these two parameters may be more complex than currently described in empirical studies.

We noticed that a more sensitive striatal dependence on dopamine may regulate the system, diminishing, although not completely eliminating, the OCD signs. This is in agreement with hypothesis $H3$, associating OCD with a weaker dopamine modulation of the ventral striatum.

Finally, we further investigated the role of the amygdala, a key regulator of arousal, in obsessive–compulsive mechanics. A classical and intuitive view would be that a weaker inhibition of the amygdala (either internal or from external sources, such as cortical areas) would result in higher amygdalar activation, and subsequently in higher

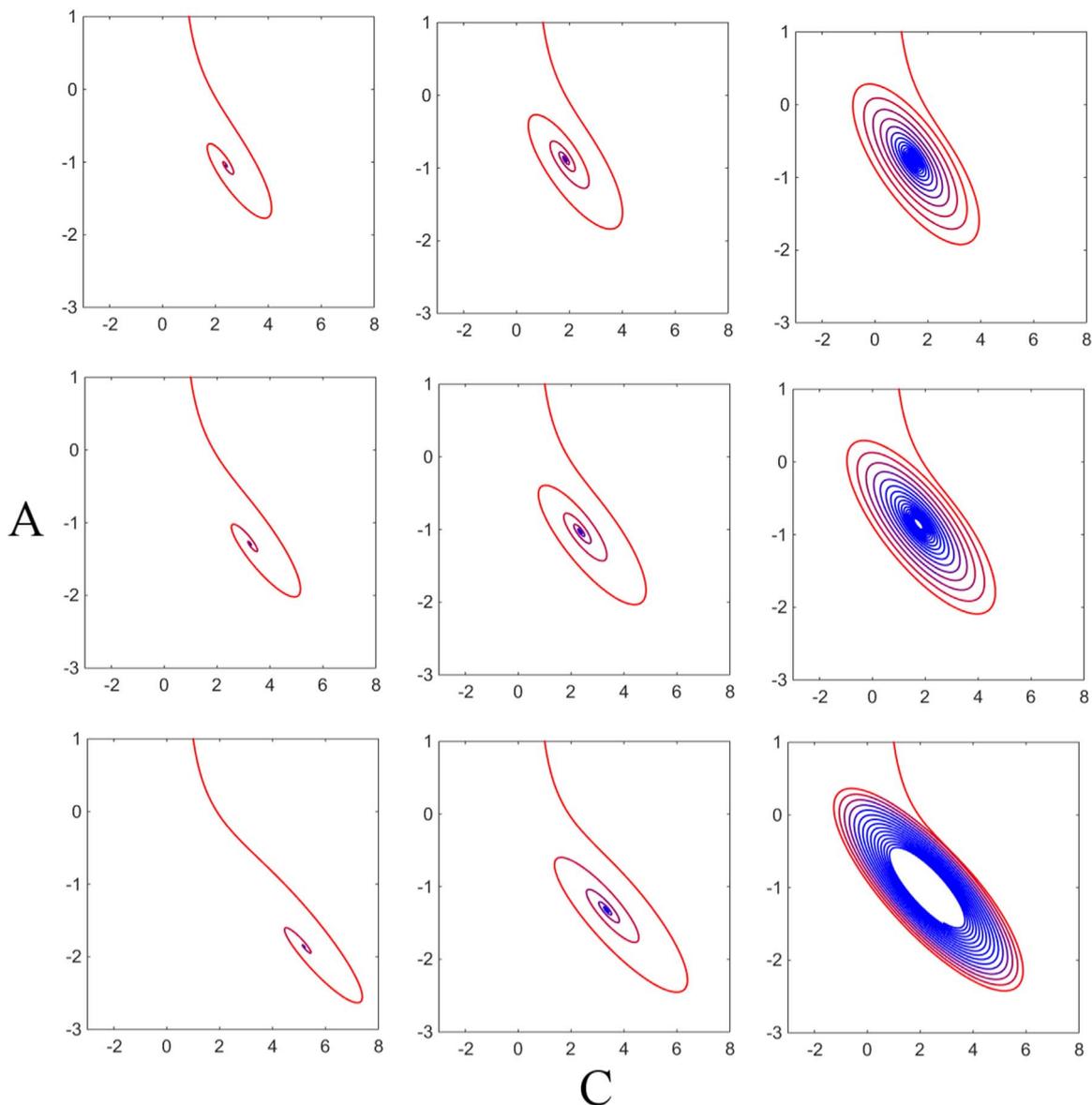


Fig. 3. Attracting states of the system for different values of the connectivities b_1 and b_2 . All panels show the evolution of a typical trajectory in a (C,A) slice. The simulations were produced for $\lambda = 0.2$ (representing higher dopamine modulation of the NAc). Each row shows a different b_1 value: $b_1=0.4$ (top); $b_1=0.8$ (middle); $b_1=1.2$ (bottom). Each column shows a different b_2 value: $b_2=0.4$ (left); $b_2=0.8$ (center); $b_2=1.2$ (right). Other parameter values: $m=1$, $n=1.4$, $a=2$, $\mu = 0.1$.

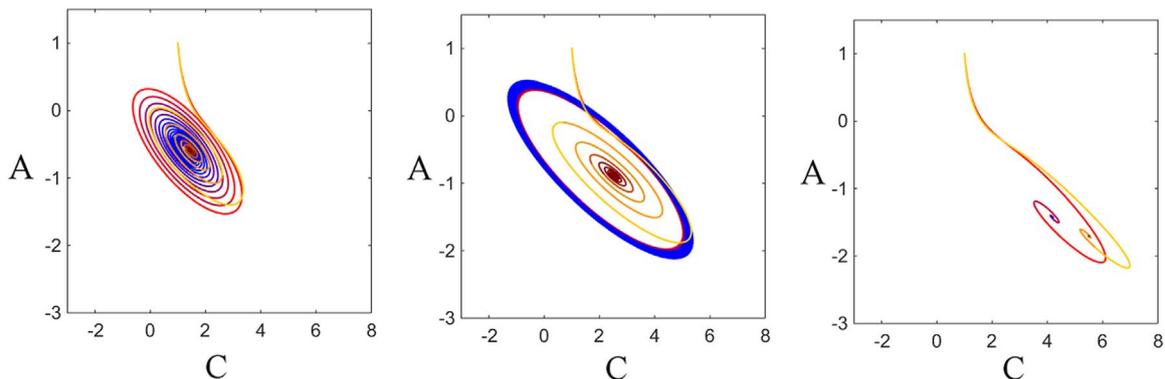


Fig. 4. Attracting states of the system for different values of amygdala self-inhibition n_A . In each panel, the evolution of trajectories in the (A,C) slice is shown for lower amygdala self-inhibition $n_A=1.4$ (from red to blue) and for higher $n_A=1.6$. The three different panels represent three different combinations of (b_1, b_2) : $b_1=0.4, b_2=1.2$ (left); $b_1=1.2, b_2=1.2$ (center); $b_1=1.2, b_2=0.4$ (right). Other parameter values: $m=1, n=1.4, a=2, \mu = \lambda = 0.1$. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

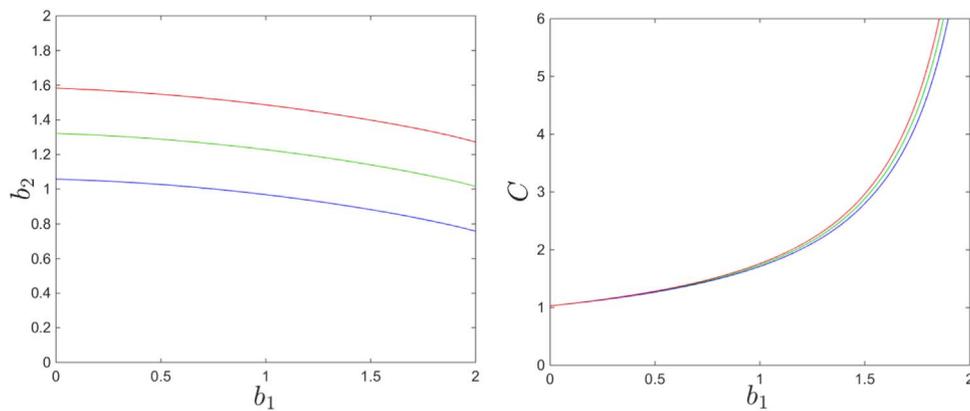


Fig. 5. Position of the Hopf curve as n_A is varied. Left: The Hopf curves with respect to b_1 and b_2 , for $n_A=1.2$ (blue), $n_A =1.4$ (green) and $n_A=1.6$ (red) are plotted in the (b_1, b_2) parameter plane. Right: The same curves, for the same values of n_A and with the same color coding, are plotted in a (b_1, C) slice, to illustrate the steady state value of C at the transition between regimes. Other parameter values: $m=1, n=1.4, a=2$. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

anxiety. We found that to be a rather simplistic view, and that, as expected, the effect depends on contributions from other areas, and cannot be judged in absence of more global information on the system.

For example, when operating in a “normal” range of OFC-Nac and A-Nac connectivity, increasing amygdalar self-inhibition has a stabilizing effect (e.g., produces faster convergence of trajectories to a well-controlled equilibrium). This effect is even more dramatic when the system is operating in a range with abnormally high OFC-Nac connectivity, but normal A-Nac connectivity, where a similar increase in amygdala self-inhibition can stop an obsessive-compulsive oscillation and stabilize it to a stable equilibrium within the normal functional range. For high OFC-Nac connectivity in conjunction with low A-Nac connectivity (both described in the literature as factors contributing to OCD symptoms), increasing amygdalar self-inhibition increased ACC asymptotic levels and enhanced quite dramatically the compulsion behavioral aspect.

Similarly, when increasing the cortical inhibition of the amygdala, the effects also differed between the three situations. When under low OFC-Nac and high A-Nac, increasing inhibition only introduced slight changes in the position of the attractor and the evolution path towards it. For high OFC-Nac and high A-Nac, increased inhibition did not break the obsessive compulsive oscillation, but rather changed its geometry, emphasizing larger oscillations along the amygdala axis and lower amplitude along the cingulate axis (i.e., behavior governed more by mood swings than by variations in compulsive behavior). Finally, for high OFC-Nac and low A-Nac, higher inhibition surprisingly reduced cingulate levels, with slightly increasing amygdala levels (that is, the regime sports higher anxiety levels at the expense of reducing

compulsions). This is precisely the opposite effect to that of increasing amygdala self-inhibition under otherwise the same circumstances.

In conclusion, our analysis shows that changes in parameters *can* be responsible for the system operating in different dynamic ranges. We found all hypotheses investigated to correspond to realizable scenarios that may lead to triggering OCD behavior or contributing to worsening of symptoms. However, it would be a mistake to consider these factors out of context and in isolation, since each describes a different aspect of the elephant that fills the room, and only in combination could they shed light on the problem as a whole. In addition, connectivity changes are dynamic and fluid, hence our connectivity parameters should also change along with the system's states—not being adjusted by hand, but rather allowing the system itself to adjust them as it evolves. It is precisely in this direction that mathematical models can provide crucial support. Obtaining tractable biophysical, data-driven models of the reward/executive network may lead to major advances of our knowledge of the causes of OCD.

Our study in particular has qualities such as computational tractability, generality (in the sense that similar setups can be used towards testing additional hypotheses about function in this network, as well as in other regulatory loops). We hope that this framework may help other investigators build upon our approach to further address such questions.

However, the model also has clear limitations. One main qualitative imposition on our system is the linearity of excitatory and inhibitory influences between brain areas. While this first order approximation is a convenient simplification to use in conjunction with linear connectivity parameters computed from empirical data—it is a course model-

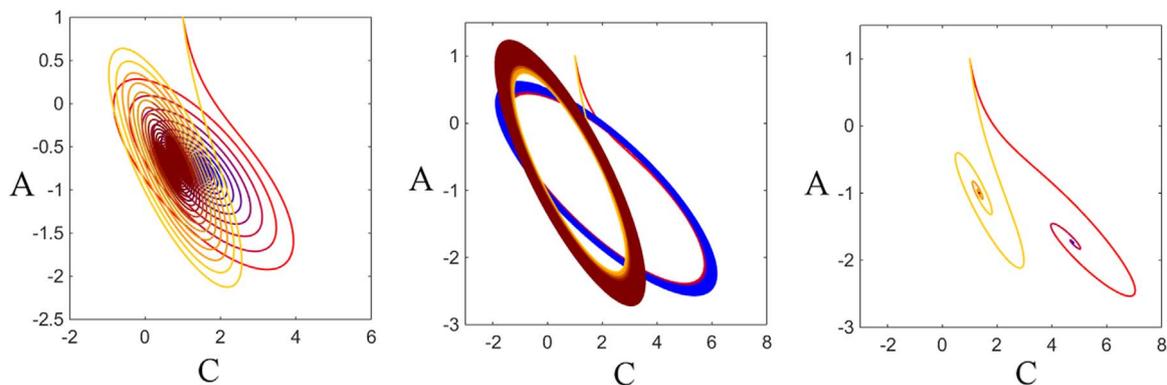


Fig. 6. Attracting states of the system for different values of the cortical inhibition of the amygdala a . In each panel, the evolution of trajectories in the (A,C) slice is shown for lower inhibition $a=2$ (from red to blue) and for higher inhibition $a=2.5$. The three different panels represent three different combinations of (b_1, b_2) : $b_1=0.4, b_2=1.2$ (left); $b_1=1.2, b_2=1.2$ (center); $b_1=1.2, b_2=0.4$ (right). Other parameter values: $m=1, n = n_A = 1.4, \mu = \lambda = 0.1$. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

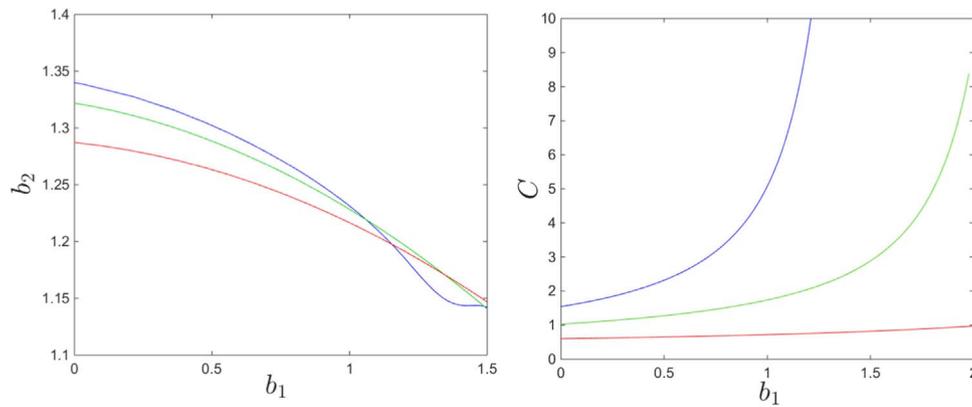


Fig. 7. Position of the Hopf curve as α is varied. Left. The Hopf curves with respect to b_1 and b_2 , for $\alpha=1.8$ (blue), $\alpha=2$ (green) and $\alpha=2.5$ (red) are plotted in the (b_1, b_2) parameter plane. Right. The same curves, for the same values of α and with the same color coding, are plotted in a (b_1, C) slice, to illustrate the steady state value of C at the transition between regimes. Other parameter values: $m=1$, $n_A = n = 1.4$. (For interpretation of the references to color in this figure caption, the reader is referred to the web version of this paper.)

ing assumption, which can be refined in future work. Another limitation of our model is its phenomenological aspect—part of our current work is directed towards estimating ranges of empirical values for the system's parameters, allowing more realistic classifications and predictions of possible behaviors. Finally, our model is conceived at a single spatio-temporal scale, that are regions of interest, with the networked brain areas viewed as black boxes (consistent with the perspective offered by imaging studies). This approach does not address neural activity and synaptic patterns, the biophysical level where the mechanics of OCD actually happens. We are currently working on a neural model of the cortico-striato-thalamo-cortical loop, based on population excitatory/inhibitory interactions. A multi-scale neural model obtained by merging these two complexity levels would incorporate the crucial neurobiology, yet allow, via a neuro-vascular filter, comparison with BOLD empirical data from fMRI scans of OCD patients.

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