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Special Issue: Cognition in Neuropsychiatric Disorders

A neurocomputational approach to obsessive-compulsive disorder

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A recent article shows that a change in a single parameter in a neural-network model of brain dynamics leads to repetitive behaviors that resist termination and towards which the network tends. These findings may have implications for obsessive-compulsive disorder and are consistent with evidence of glutamatergic hyperactivity in this disorder.

The use of neurocomputational models to understand the neural substrates of cognition and behavior has become widespread over the last 25 years. For many years, however, the application of such models to psychiatric disorders was more limited than it arguably should have been, despite notable early successes [1] and some continued efforts in this area over the years [2]. Recently, however, this area has been growing rapidly [3–5]. Neurocomputational models offer substantial advantages for psychiatry, as they focus on neural mechanisms and provide an integrated understanding of phenomena occurring at different levels (e.g., bridging from synaptic abnormalities to their effects on behavior). Such mechanistic, integrative understanding – which other computational approaches (e.g., normative ones) do not always provide – is crucial to understand the mechanism of action of current brain-based treatments and for the rational development of new ones.

A recent example of the usefulness of applying neurocomputational models to psychiatry comes from a model by Verduzco-Flores *et al.* [6] that may foster new insights into obsessive-compulsive disorder (OCD). OCD is a debilitating disorder typically characterized by the presence of both obsessions (intrusive, repetitive, and persistent thoughts) and compulsions (repetitive behaviors or mental acts). The most prominent large-scale neural abnormalities in OCD involve key structures in the limbic cortico-basal ganglia-thalamo-cortical loop: the orbitofrontal cortex, anterior cingulate cortex, and caudate nucleus [7]. However, the specific microcircuit abnormalities that give rise to OCD remain unknown. The model by Verduzco-Flores *et al.* may help shed light on which such abnormalities may give rise to repetitive and persistent thoughts and behaviors – the core symptoms of OCD and related disorders such as Tourette syndrome (TS).

Verduzco-Flores *et al.* characterize their model as a model of 'working memory'. We will interpret the model more broadly, as the evidence that OCD involves disturbances in working memory *per se* is somewhat limited. What matters for our purposes is that their model can quickly learn a sequence and maintain it active, repeatedly cycling through it. Under normal operation, when a new sequence is presented to the network, the network shifts from maintaining the old sequence to maintaining the new sequence. Similarly, when the network is presented with a 'termination' signal, it stops representing the prior sequence. This ability to learn and actively maintain sequences and to flexibly shift between sequences or terminate them when necessary is probably useful for many cognitive and motor functions. The relevance of this work for OCD is that under a simple parameter manipulation, the network becomes unable to shift from or terminate certain sequences, thereby exhibiting repetitive patterns of activity that persist long after they are appropriate – much like obsessions and compulsions.

Verduzco-Flores *et al.*'s model is fairly abstract, as it consists simply of one population of excitatory units and one of inhibitory units. The excitatory units are all mutually connected; the connectivity between excitatory and inhibitory units is moderately dense in both directions. The parameter manipulation that results in sequences becoming 'stuck', repeating again and again, is a reduction in inhibition. Furthermore, if such reduction affects mostly one or a few sequences, the network activity tends to get attracted to that sequence or sequences, much like patients with OCD tend to gravitate towards specific obsessions and compulsions. In addition, under reduced inhibition, sequences sometimes merge, forming longer sequences, which might help explain why rituals in OCD tend to become more and more elaborate.

Reduced inhibition does not map well to any known disturbance in OCD. However, what likely matters in the model is the balance between excitation and inhibition. Thus, the same pathological dynamics should occur with increased excitation, and that would be highly consistent with evidence of glutamatergic hyperactivity in OCD [8]. In fact, prior modeling has shown that glutamatergic hyperactivity produces 'overstable' attractor states that are difficult to escape and that could therefore underlie the 'stickiness' that characterizes OCD [9]. The article by

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Verduzco-Flores *et al.* is along similar lines but extends that work to sequences, which may better capture the ritualistic, stereotyped character of OCD.

Verduzco-Flores *et al.* characterize their model as a model of cortical dynamics, but the model is abstract and so is probably best viewed as demonstrating the importance of the balance between excitation and inhibition for the controllability of sequences of thoughts or behaviors, without constraining hypotheses as to the specific locus or loci of origin of the imbalance in OCD. Such imbalance could have cortical origin, but it could also be due, for example, to an imbalance between direct and indirect basal-ganglia pathways, which are disinhibitory and inhibitory, respectively [3]. In fact, the basal ganglia have been implicated in sequence learning and in sequential and ritualistic behaviors [10], as well as in OCD [7]. The primary site of dysfunction in OCD therefore remains unknown, and it could even vary across patients [7].

The article by Verduzco-Flores *et al.* does have important limitations. For example, it argues that reduced inhibition explains both OCD and several symptoms of schizophrenia unrelated to OCD. What, then, distinguishes these disorders? Furthermore, the parameter manipulations tried – which included several others in addition to reduced inhibition – seem arbitrary, lacking justification in terms of known disturbances in the disorders addressed. In fact, even the relation of the results to glutamatergic hyperactivity in OCD is not made explicit in the article.

Despite these limitations, the article by Verduzco-Flores *et al.* could meaningfully contribute to an understanding of OCD and other disorders. Other investigators have used related approaches to model aspects of the neural dynamics underlying OCD [9] and other disorders [4], but Verduzco-Flores *et al.* extend that work from the simple domain of fixed-point attractors to the domain of complex attractor sequences. Given the prevalence of rigid and repetitive cognitive and behavioral routines not only in OCD but also in other disorders (e.g., TS and autism), the advances in Verduzco-Flores *et al.* could open new opportunities for neurocomputational models to further our understanding of several disorders.

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Insights for treatment in Tourette syndrome from fMRI

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In a recent *American Journal of Psychiatry* article, Wang and colleagues used functional MRI (fMRI) to examine cortico-striatal-thalamo-cortical circuitry in Tourette syndrome (TS), advancing the field's investigation of circuit level dysfunction *in vivo* in individuals with TS. Their results provide insight for interrogating neural mechanisms underlying different treatment methods.

Tourette syndrome (TS) is a common developmental disorder of the central nervous system characterized by motor and vocal tics. Tics are involuntary, brief, stereotyped movements and/or vocalizations that range in severity across affected individuals. Tics are commonly preceded by a sensory 'premonitory urge' that is briefly relieved by the performance of a tic. Current neurobiological models of TS posit dysfunction of the basal ganglia and its related structures, specifically cortico-striatal-thalamo-cortical (CSTC) circuits, as the source of tic behavior [1]. Individual regions comprising these circuits have been implicated in a number of neuroimaging (positron emission tomography, structural MRI, fMRI) studies of TS. However, interrogating the relationships between these regions, which would provide insight into the circuitry, is challenging using such neuroimaging techniques. In a recent paper, published ahead of print in the *American Journal of Psychiatry*, Wang *et al.* [2] employed fMRI and advanced statistical techniques to interrogate the involvement of regions within CSTC circuitry during tic behavior, and to investigate functional relationships between those regions.

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