CHAPTER

1

Cortical Circuit Models in Psychiatry: Linking Disrupted Excitation–Inhibition Balance to Cognitive Deficits Associated With Schizophrenia

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1.1 INTRODUCTION

Ultimately, a central goal of neuropsychiatric research is to explain how symptoms and cognitive deficits arise from neurobiological pathologies. At present, we do not yet adequately understand how a neural system generates complex symptoms of any psychiatric disorder. This is in large part due to the stark explanatory gaps between levels of analysis: mechanisms underlying a psychiatric disease occur at the level of neurons and synapses, whereas symptoms are manifested and diagnosed at the level of cognition and behavior, which involve collective computations in brain circuits. Linking these levels is vital for gaining mechanistic insight into mental illness, and for the rational development of pharmacological treatments, which have physiological impact at the biophysical level. An emerging interdisciplinary approach to this challenge, "computational psychiatry," uses mathematical models of neural systems, in close interplay with experimentation, to study how disruption at lower levels propagate upward to produce dysfunction at higher levels of behavior and function (Wang and Krystal, 2014; Anticevic et al., 2015; Huys et al., 2016).

Biophysically based neural circuit modeling is a framework particularly well suited to link synaptic-level disruptions to emergent brain dysfunction. Circuit models can simulate neural population activity and computations, incorporating key properties of neurons, synapses, and circuit connectivity. Dynamic neural activity can be simulated through systems of differential equations governing the biophysical properties of neurons and synapses. Emergent patterns of activity in the model can be informed by—and tested with—empirical measures of neural activity. In

certain circuit models, neural activity can be mapped onto a behavioral response, thereby generating model predictions that can be tested with behavioral data from corresponding task paradigms. Neural circuit models can play a key role in translational neuroscience, because by virtue of their biophysical basis such models provide opportunities to mechanistically understand how synapse-level disruptions produce aberrant neural activity and deficits in cognition and behavior.

In this chapter, we focus our review on a set of studies that leverage biophysically based neural circuit models to understand how synaptic disruptions may induce cognitive deficits, with particular relevance to schizophrenia (Murray et al., 2014; Starc et al., 2017; Lam et al., 2017). These studies thereby provide a test bed for a computational psychiatry framework utilizing biophysically based neural circuit modeling. Specifically, we utilized spiking circuit models of microcircuits in association cortical areas (such as the prefrontal cortex and posterior parietal cortex), which can perform two core cognitive functions, working memory, and decision making (Compte et al., 2000; Wang, 2002). These models were developed to capture key neurophysiological correlates of cognitive function in association cortex and have been validated through their predictions for cognitive behavior, neural activity, and synaptic mechanisms. We applied these models to study the impact of alterations in the balance between synaptic excitation and inhibition (E/I) balance (Hensch and Fagiolini, 2004). Altered E/I balance is hypothesized to contribute to pathophysiological states across a number of neuropsychiatric disorders such as schizophrenia. Cognitive deficits, including in working memory and decision making, lie at the core of schizophrenia (Elvevåg and Goldberg, 2000). Yet it remains poorly understood how they may relate to the hypothesized neuropathological alterations such as disrupted E/I balance.

For both working memory and decision making, we found that relatively small perturbations of the E/I ratio in the models can profoundly impact cognitive function. Importantly, the models make dissociable predictions—testable at the level of cognitive behavior—for elevated versus lowered E/I ratio. These modeling studies illustrate general principles for computations in recurrent cortical circuits and elucidate distinct modes of cognitive dysfunction in disease-related states. This test bed for computational psychiatry can be applied to other disorders and other cognitive functions. Furthermore, we argue that to be most useful in computational psychiatry, neural circuit modeling should go hand in hand with basic neuroscience research by integrating findings into a formal model and making testable predictions, which can inform the design and analysis of experiments in animals and humans. Neural circuit models can thereby play a key translational bridge across various levels of analysis, spanning biophysics, systems neurophysiology, and cognitive neuroscience applied to clinical populations.

1.2 ROLES FOR BIOPHYSICALLY BASED NEURAL CIRCUIT MODELING IN COMPUTATIONAL PSYCHIATRY

From a computational psychiatry perspective, biophysically based neural circuit modeling can address key questions that are inaccessible to other levels of computational modeling, such as connectionist models or normative mathematical models of behavior (Wang and Krystal, 2014; Anticevic et al., 2015; Huys et al., 2016). For instance, circuit models are well suited to mechanistically study the impacts of synapse-level alterations. One can perturb specific synaptic parameters in the model that are physiologically interpretable, thereby allowing direct implementation of hypothesized perturbations related to disease mechanisms and pharmacological manipulations. One can then characterize the impact of these perturbations on emergent neural activity and behavior, and relate them to experimental findings from healthy and clinical populations as well as in animal models of disease states. Biophysically based models may also be able to inform the rational design of pharmacological therapies, by mechanistically linking molecular, cellular, circuit, and ultimately behavioral levels of analysis.

The specific scientific questions under study play a critical role in determining the level of biophysical detail included in a particular model. Circuit models typically incorporate certain biophysical details but not many others. For instance, some questions related to how dopaminergic dysregulation in schizophrenia impacts synaptic transmission could be addressed in a biophysically based model of an individual synapse that includes subcellular signaling pathways (Qi et al., 2010). In contrast, emergent circuit-level dynamics, such as oscillations or persistent activity, can be simulated in thousands of recurrently connected spiking neurons whose individual dynamics are simplified to include only certain channels and receptors (Wang, 2010, 2008). Modeling systems-level disturbances, such as large-scale connectivity alterations in schizophrenia, may entail coarse-grained mean-field models of local nodes organized in large-scale networks that still contain neurophysiologically interpretable parameters and enable study of questions related to E/I balance (Yang et al., 2014, 2016a).

An important area of research in clinical neuroscience is the discovery and characterization of predictive neurophysiological biomarkers for psychiatric disorders. Models can inform the circuit mechanisms underlying these biomarkers and their relations to putative synaptic disruptions. These biomarkers can include electrophysiological measurements of aberrant neural oscillatory dynamics and neuroimaging measurements of large-scale dysconnectivity in resting-state activity. Insofar as the circuit model is well constrained and validated through experiments, dissociable model predictions allow interpretation of biomarkers to

generate mechanistic hypotheses for future experimental studies in animal models and human subjects.

One area of modeling progress with relevance to biomarkers explores the mechanisms underlying oscillatory neural activity that emerge at the network level in recurrent cortical circuits (Wang, 2010). Cortical oscillatory activity is found to be abnormal in a number of neuropsychiatric disorders. In particular, schizophrenia is associated with alterations in oscillatory activity in the gamma (30−80 Hz) range (Gonzalez-Burgos and Lewis, 2012; Uhlhaas, 2013). Computational models, in conjunction with physiological findings, support the idea that neocortical gamma oscillations arise from a feedback loop in a microcircuit of pyramidal cells reciprocally connected to perisomatic-targeting, parvalbumin-expressing interneurons (Buzsáki and Wang, 2012). Circuit models of gamma oscillations have been applied to explore the dynamical effects of putative synaptic perturbations associated with schizophrenia, including reduced production of γ-aminobutyric acid (GABA) and parvalbumin in inhibitory interneurons (Vierling-Claassen et al., 2008; Spencer, 2009; Volman et al., 2011; Rotaru et al., 2011). In each case, the models have provided specific hypotheses for how systems-level dynamics, which can be measured in humans through techniques such as electroencephalography (EEG) or magnetoencephalography (MEG), may be altered as a result of synaptic- or cellular-level changes.

Below, we focus on how circuit models of cognitive functions can be applied to understand cognitive deficits resulting from synaptic disruptions associated with schizophrenia. For certain core cognitive computations, we have knowledge of the neural circuit basis underlying these processes, which typically involve contributions from animal studies. For these cases, detailed circuit models can be developed rigorously to provide the link from synaptic disruptions to behavior (e.g., cognitive deficits discussed below). In other cases, psychiatric symptoms relate to complex cognitive functions for which we lack understanding of the underlying neuronal representations or circuit mechanisms. At present, these circuit models are limited and cannot be applied to complex behavioral tasks, for which we lack understanding of neural circuit correlates. We now turn to the conditions in which circuit models may be best suited to study cognitive deficits in psychiatric disorders.

1.3 LINKING PROPOSITIONS FOR COGNITIVE PROCESSES

A major goal in computational psychiatry research is for biophysically based neural circuit models to explain mechanistically how synaptic-level disruptions induce cognitive-level deficits. We argue that for this

approach to be most effective, the circuit model should be grounded in a well-supported relationship between neuronal activity and a given cognitive process. Such relationships have been formalized by the concept of a *linking proposition* that states the nature of a statistical correspondence between a given neural state and a cognitive state. Related to the concept of the linking proposition is that of a *bridge locus*, which is the set of neurons for which this linking proposition holds (Teller, 1984). Convergent evidence supporting a linking proportion comes from a number of experimental methodologies applied to animal models, especially to behaving nonhuman primates, given the strong homologies of areas in the human and nonhuman primate brains (Schall, 2004). Single-neuron recordings can relate neuronal activity to computations posited in psychological processes. Further evidence can come from perturbative techniques such as microstimulation or inactivation.

As an exemplary application of this perspective to a nonsensory function, Schall (2004) considered the neural underpinnings of the preparation of saccadic eye movements. In the case of saccade preparation, a well-supported candidate for the bridge locus is a distributed network of cortical and subcortical areas, including the frontal eye field and superior colliculus. During saccade preparation, so-called "movement" neurons in these areas exhibit a location-selective ramping of their firing rates, and a saccade is initiated when their firing rates reach a threshold level. At the level of mental processes, a leading psychological model for response preparation is accumulation of a signal until reaching a fixed threshold level, which triggers the response. In such accumulator models, sequential sampling of a stochastic signal generates variability in the rate of rise to the fixed threshold, which can explain the observed variability in saccade reaction times. The linking proposition between a neural state (movement cell firing rates) and a psychological state (level of an accumulator) provides a framework for detailed hypothesis generation and experimental examination of psychological models.

What linking propositions do we have for core cognitive functions, and specifically for working memory and decision making? The neural correlates of working memory have been studied extensively through single-neuron recordings from monkeys performing tasks in which the identity of a transient sensory stimulus must be maintained internally across a seconds-long mnemonic delay to guide a future response. These studies revealed that a key neural correlate of working memory is stimulus-selective persistent activity, i.e., stable elevated firing rates in a subset of neurons that spans the mnemonic delay (Goldman-Rakic, 1995; Wang, 2001). These neuronal activity patterns are observed across a distributed network of interconnected brain areas with prefrontal cortex as a key locus. For instance, in one well-studied experimental paradigm, the oculomotor delayed response task, the subject must maintain in working memory the spatial location of a visual cue across a delay period to guide a saccadic eye movement toward that location

(Funahashi et al., 1989). During the mnemonic delay, a subset of prefrontal neurons exhibit stimulus-tuned persistent activity patterns, with single neurons firing at elevated rates for a preferred spatial location. These neurophysiological findings have grounded the leading hypothesis that working memory is supported by stable persistent activity patterns in prefrontal cortex that bridge the temporal gap between stimulus and response epochs.

The neural computations underlying decision making have been most studied in task paradigms in which a categorical choice is based on the accumulation of perceptual evidence over time. In one highly influential task paradigm, the subject must decide the net direction of random-dot motion stimuli, which encourages decision making based on the temporal integration of momentary perceptual evidence (Roitman and Shadlen, 2002). Behavior can be well captured by psychological process models of evidence accumulation to a threshold. Single-neuron recordings have found that in association cortex, such as the lateral intraparietal area, choice-selective ramping of neuronal firing rates reflects accumulated perceptual evidence, with activity crossing a threshold level reflecting the decision commitment (Gold and Shadlen, 2007). These neural correlates reflect two key computations needed for perceptual decision making: accumulation of evidence and formation of categorical choice.

Conceptually, a neural circuit model can instantiate a linking proposition for a cognitive process and propose circuit mechanisms underlying the computations. If associated with a hypothesized bridge locus, model predictions for these circuit mechanisms can be experimentally tested, such as through single-neuron recordings. For instance, in the case of working memory, experiments have tested how focal antagonism of specific synaptic receptors affects persistent activity, thereby informing the neuronal and synaptic mechanisms supporting the computations (Wang et al., 2013; Rao et al., 2000). The stronger these links are among (1) the synaptic and neuronal processes in circuit mechanisms, (2) neural activity, and (3) the cognitive function, the greater the potential for translational computational psychiatry. Once established, the model can then make rigorous predictions for the consequences of alterations in those circuit mechanisms. In this way, circuit models can iteratively contribute to our understanding of these links across levels of analysis and leverage them to study dysfunction in neuropsychiatric disorders.

1.4 ATTRACTOR NETWORK MODELS FOR CORE COGNITIVE COMPUTATIONS IN RECURRENT CORTICAL CIRCUITS

Biophysically based neural circuit modeling has provided mechanistic hypotheses for how working memory and decision making computations can be performed in recurrent cortical circuits (Wang, 2001, 2008).

As noted, a key neurophysiological correlate of working memory is stimulus-selective, persistent neuronal activity across the mnemonic delay in association cortical areas. Delays in working memory tasks (a few seconds) are longer than the typical timescales of neuronal or synaptic responses (10−100 ms). Similarly, perceptual decision making demands categorical selection and benefits from temporal integration of evidence over long timescales (hundreds of milliseconds). Both of these computations therefore implicate circuit mechanisms.

Motivated by experimental observations of stable persistent activity in single neurons, a leading theoretical framework proposes that working memory-related persistent activity states are dynamical attractors, i.e., stable states in network activity. In the mathematical formalism of dynamical systems, an attractor state is an activity pattern that is stable in time, so that following a small transient perturbation away from this state the network will converge back to the attractor state. A class of neural circuit models called attractor networks have been applied to explain the mechanisms that allow a recurrent network of spiking neurons to maintain persistent activity during working memory (Amit, 1995; Wang, 2001). An attractor network typically possesses multiple attractor states: a low-firing baseline state and multiple memory states in which a stimulus-selective subset of neurons are persistently active. Because the memory state is an attractor state, it is self-reinforcing and resistant to noise or perturbation by distractors, allowing the stimulus-selective memory to be stably maintained over time (Brunel and Wang, 2001; Compte et al., 2000).

In a typical attractor network, subpopulations of excitatory neurons are selective to different stimuli. Recurrent excitatory synaptic connectivity exhibit a "Hebbian" pattern such that neurons of similar selectivity have stronger connections between them (Fig. 1.1A). When the strength of recurrent excitatory connections is strong enough, the circuit can support stimulus-selective attractor states that can subserve working memory (Fig. 1.1B). Strong recurrent excitation thereby provides the positive feedback that sustains persistent activity. Wang (1999) found that incorporating physiologically realistic synaptic dynamics pose constraints on the synaptic mechanisms supporting this positive feedback. Strong positive feedback is prone to generate large-amplitude oscillations that can destabilize persistent states and can drive firing rates beyond physiologically plausible ranges. It was found that both of these problems can be solved if recurrent excitation is primarily mediated by slow N-methyl-D-aspartate (NMDA) receptors.

Critically, recurrent excitation must be balanced by strong feedback inhibition mediated by GABAergic interneurons. Feedback inhibition stabilizes the low-activity baseline state (Amit and Brunel, 1997; Wang, 1999). In a persistent activity memory state, lateral inhibition enforces selectivity of the working memory representation, preventing the spread
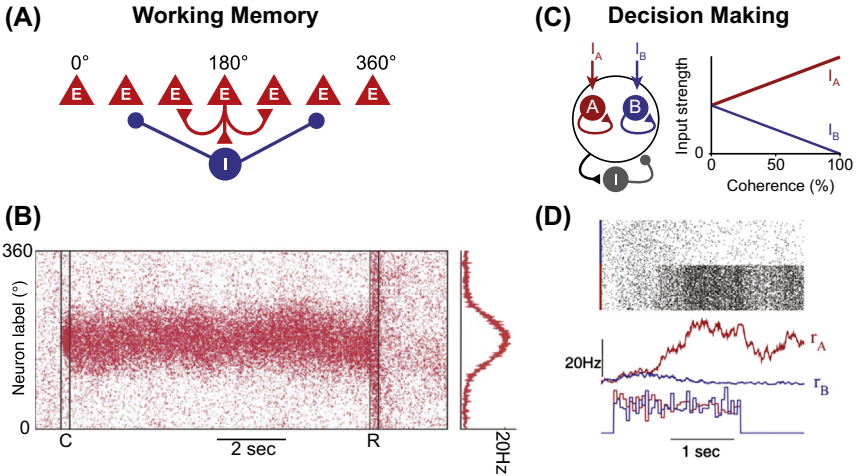
FIGURE 1.1 Biophysically based cortical circuit models of working memory and decision making computations. (A) Schematic of the network architecture for a model of spatial working memory. The model consists of recurrently connected excitatory pyramidal cells (E) and inhibitory interneurons (I). Pyramidal cells are labeled by the angular location they encode (0−360 degrees). Excitatory-to-excitatory connections are structured, such that neurons with similar preferred angles are more strongly connected. Connections between pyramidal cells and interneurons are unstructured and mediate feedback inhibition. (B) Spatiotemporal raster plot showing a bump attractor state in an example trial. A stimulus is presented at 180 degrees during the brief cue epoch (denoted C) and during the subsequent delay; the stimulus location is encoded by persistent activity throughout the working memory delay until the response epoch (denoted R). On right is shown the firing rate profile of the working memory bump attractor state. (C) Schematic of the network architecture for a model of perceptual decision making. The circuit contains two populations of pyramidal neurons which are each selective to one of the two stimuli (A and B). Within each pyramidal-neuron population there is strong recurrent excitation, and the two populations compete via feedback inhibition mediated by interneurons (I). Right: The selective populations receive sensory-related inputs determined by the stimulus coherence. (D) Example neuronal activity in a single trial for a zero-coherence stimulus. Top: Spatiotemporal raster plot for the two selective populations. Middle: Population firing rates r_A and r_B. Bottom: Stochastic sensory-related inputs. During decision making, the circuit exhibits an initial slow ramping, related to temporal integration of evidence, which leads to categorical choice (for A in this trial). *Panels (B and D) adapted from Compte, A., Brunel, N., Goldman-Rakic, P.S., Wang, X.-J., 2000. Synaptic mechanisms and network dynamics underlying spatial working memory in a cortical network model. Cereb. Cortex 10, 910−923; Wang, X.-J., 2002. Probabilistic decision making by slow reverberation in cortical circuits. Neuron 36, 955−968, respectively.*

of excitation to the entire neuronal population (Murray et al., 2014). Attractor dynamics supporting working memory are thereby supported by recurrent E/I that are strong and balanced. These circuit models make predictions for the relationship between synaptic mechanisms and working memory activity, which are confirmed through experiments combining single-neuron recording and pharmacological manipulation in

prefrontal cortex. Locally blocking excitation mediated by NR2B NMDA receptors attenuates persistent activity for the preferred stimulus (Wang et al., 2013). Locally blocking inhibition mediated by GABA$_A$ receptors reduces stimulus selectivity of delay activity by elevating responses to nonpreferred stimuli (Rao et al., 2000).

In addition to working memory computations, strong recurrent excitatory and inhibitory connections in cortical attractor networks provide a circuit mechanism for decision making, supporting temporal integration of evidence, and categorical choice (Wang, 2002, 2008; Wong and Wang, 2006). In this model, choice-selective neuronal populations receive external inputs corresponding to sensory information (Fig. 1.1C). Reverberating excitation enables temporal accumulation of evidence through slow ramping of neural activity over time (Fig. 1.1D). This property highlights that attractor networks not only support multiple stable states (representing categorical choices), but also support slow transient dynamics that can instantiate computations such as temporal integration. In these models, temporal integration via recurrent excitation benefits from the slow biophysical timescale of NMDA receptors (Wang, 2002). Feedback and lateral inhibition mediated by GABAergic interneurons mediates competition among neuronal populations underlying the formation of a categorical choice. Irregular neuronal firing, a ubiquitous feature of cortex, contributes to stochastic choice behavior across trials, even when presented with identical stimulus inputs.

These computational modeling studies demonstrate that an association cortical microcircuit model can support working memory and decision making computations through attractor dynamics. This therefore suggests a shared "cognitive-type" circuit mechanism for these functions, which may provide components on which more complex cognitive processes may be built (Wang, 2013). Because these functions rely on strong recurrent E/I, they are particularly well suited to study how cognitive deficits may arise from alterations in synaptic function, which are implicated in neuropsychiatric disorders.

1.5 CIRCUIT MODELS OF COGNITIVE DEFICITS FROM ALTERED EXCITATION−INHIBITION BALANCE

In a series of studies, we have applied cortical attractor network models of working memory and decision making function to characterize the impact of E/I disruptions in association cortex (Murray et al., 2014; Starc et al., 2017; Lam et al., 2017). Alteration of cortical E/I balance is implicated in multiple neuropsychiatric disorders, including schizophrenia, autism spectrum disorder, and major depression. A key strength of these circuit models is that they make explicit predictions not just for

neural activity but also for behavior, which can be tested experimentally in clinical populations or after causal perturbation.

In schizophrenia, cortical microcircuit alterations are complex, with observed dysfunction in both glutamatergic excitation and GABAergic inhibition. Postmortem investigations of prefrontal cortex in schizophrenia find reductions in spines on layer-3 pyramidal cells, which potentially reflect reduced recurrent excitation. Such studies also have revealed multiple impairments in inhibitory interneurons, which potentially reflect reduced feedback inhibition. Pharmacological manipulations provide complementary evidence. One such approach is to use NMDA receptor antagonists (e.g., ketamine), which transiently, safely, and reversibly induce cardinal symptoms of schizophrenia in healthy subjects (Krystal et al., 2003). A leading hypothesis regarding ketamine's effects on neural function proposes a state of cortical disinhibition potentially via preferential blockade of NMDA receptors on GABAergic interneurons (Greene, 2001; Homayoun and Moghaddam, 2007; Kotermanski and Johnson, 2009). However, many questions remain regarding the neural effects of ketamine, such as which NMDA receptor subunits and neuronal cell types may be the preferential sites of action (Khlestova et al., 2016; Zorumski et al., 2016).

Mechanistic links between altered E/I ratio and cognitive impairment remain tenuous. A primary motivation for these modeling studies was to formulate dissociable behavioral predictions for distinct sites of synaptic perturbation. In these studies, E/I ratio was perturbed bidirectionally via hypofunction of NMDA receptors at two recurrent synaptic sites: on inhibitory interneurons that elevates E/I ratio via disinhibition; or on excitatory pyramidal neurons that lowers E/I ratio (Fig. 1.2A).

1.5.1 Working Memory

Working memory function is a promising candidate in clinical neuroscience as an endophenotype, a quantitatively measurable core trait that is intermediate between genetic risk factors and a psychiatric disorder (Insel and Cuthbert, 2009). It is important to consider the component processes and features involved in overall working memory function: encoding, maintenance, robustness to distraction, precision, and capacity. Ongoing work in clinical cognitive neuroscience aims at resolving how these processes are impaired in schizophrenia (Barch and Ceaser, 2012). Many studies have found a deficit in working memory encoding (Lee and Park, 2005). For visuospatial working memory, patients with schizophrenia exhibit deficits in encoding and in maintenance, which results in a graded loss of precision (Badcock et al., 2008; Starc et al., 2017). Other visual paradigms find reduced capacity but not necessarily precision (Gold et al., 2010).
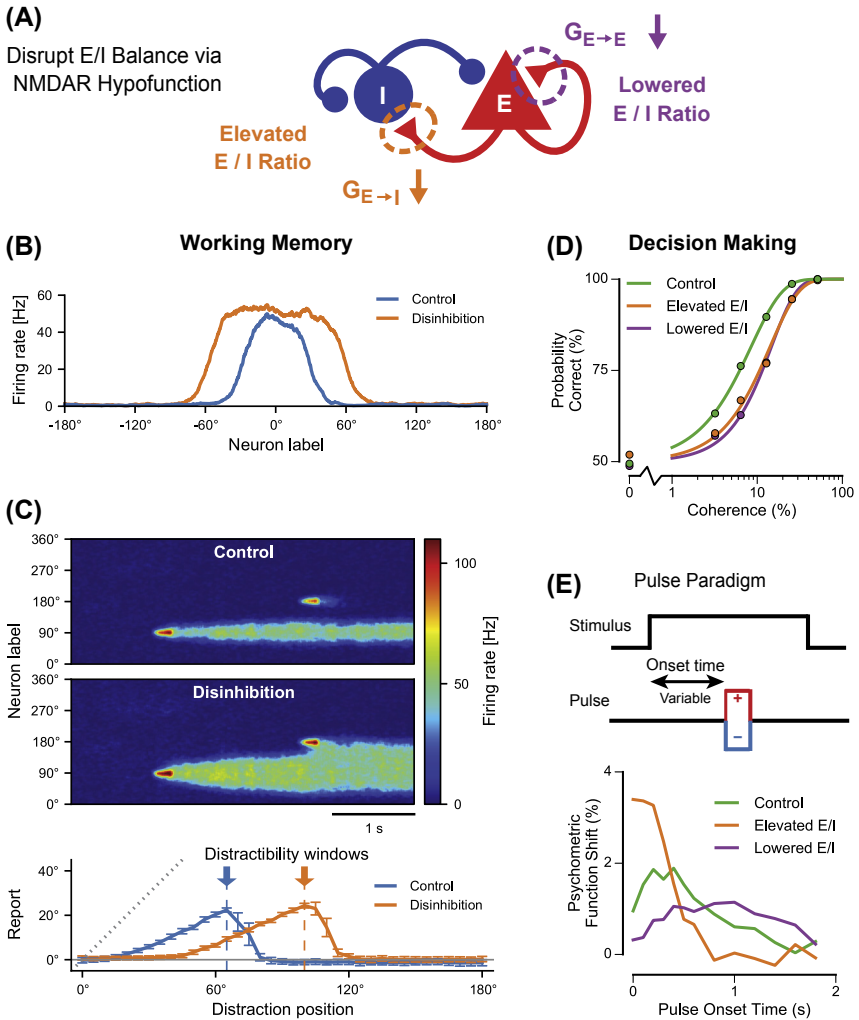
FIGURE 1.2   Effects of altered excitation−inhibition (E/I) balance in cortical circuit models of working memory and decision making. (A) E/I ratio was perturbed bidirectionally via hypofunction of NMDA receptors at two recurrent synaptic sites: on inhibitory interneurons that elevates E/I ratio via disinhibition; or on excitatory pyramidal neurons that lowers E/I ratio. (B) For the working memory circuit, the firing rate profile of the "bump" attractor activity pattern during working memory maintenance. Elevated E/I ratio via disinhibition results in a broadened working memory representation. (C) Disinhibition impairs the network's ability to filter out intervening distractors. Top: Spatiotemporal plot of network activity in response to a distractor presented during the delay at a distance of 90 degrees from the target. Bottom: Deviation of the read-out report as a function of the angular distance between the distractor and the target. The "distractibility window" is widened by disinhibition. (D) In the decision making circuit, performance as quantified by the psychometric function, i.e., the proportion of correct choices as a function of stimulus coherence. Both perturbations, elevated and lowered E/I ratio, can comparably degrade performance relative

Murray et al. (2014) examined the effects of altered E/I balance in a cortical circuit model of visuospatial working memory (Compte et al., 2000; Carter and Wang, 2007; Wei et al., 2012). Disinhibition, with results in an elevated E/I ratio, was implemented through antagonism of NMDA receptors preferentially onto interneurons. In this model, disinhibition leads to a broadening in the neural-activity patterns in the mnemonic attractor states (Fig. 1.2B). This neural change induced specific cognitive deficits. During maintenance, the mnemonic activity pattern undergoes random drift that leads to decreased precision of responses. Disinhibition increased the rate of this drift, thereby inducing a specific deficit in mnemonic precision during working memory maintenance.

Additionally, Murray et al. (2014) found that broadened neural representations make working memory more vulnerable to intervening distractors (Fig. 1.2C). In the model, a distractor is more likely to "attract" the memorandum toward it if the two representations overlap. Distractibility therefore depends on the similarity between the representations of the mnemonic target and the intervening distractor. Consistent with this model behavior, it has been found empirically that in visuospatial working memory, a distractor can attract the memory report toward its location, but only if the distractor appears within a "distractibility window" around the target location (Herwig et al., 2010). Because disinhibition broadens the mnemonic activity patterns, there is an increased range of distractors that can disrupt working memory.

To test the model prediction of broadened working memory representations under disinhibition, Murray et al. (2014) analyzed behavior from healthy humans administered ketamine during a spatial delayed match-to-sample task (Anticevic et al., 2012). The model predicted a pattern of errors depending on whether the probe was similar to a target held in working memory. Analysis of the behavioral data guided by the model revealed a similar specific pattern of errors under ketamine versus control conditions to that predicted by the computational model. Consistent with model predictions, ketamine increased the rate of errors specifically for distractors that would overlap with a broadened mnemonic representation. A similar pattern of errors has been observed in schizophrenia, with a selective increase in false alarms for near nontarget

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to the control circuit. (E) A perceptual decision making task paradigms that characterizes the time course of evidence accumulation can test dissociable behavioral predictions from elevated versus lowered E/I ratio. Top: The pulse paradigm uses a brief pulse of additional perceptual evidence at different onset times. This pulse induces a shift the psychometric function, which quantifies the sensitivity of the choice on evidence presented at that time point. Bottom: Shift in the psychometric function as a function of pulse onset time, for the three E/I regimes. Relative to control, in the elevated E/I circuit the pulse has a stronger impact at early onset times, but less impact at later onset times. The lowered E/I circuit shows a flattened profile of the shift, with greater impact at late onset times.

probes but not for far nontarget probes (Mayer and Park, 2012). In contrast to the model predictions arising from disinhibition, insufficient recurrent excitation in the model leads to a collapse of persistent activity that would induce an error pattern of misses and spatially random errors.

To apply this model to schizophrenia and more directly to test model predictions, Starc et al. (2017) designed a working memory task to be explicitly aligned with the model and with the primate electrophysiology task paradigms for which the model was developed. Such an alignment, in which the clinical study is linked to basic neurophysiology findings through a computational model, allows stronger inferences and testing of hypotheses. In the working memory task of Starc et al. (2017), the memorandum is a single visuospatial location, and the response is a direct report of the remembered location that provides a continuous measure of mnemonic coding. To test the model prediction of increased drift during working memory maintenance, the duration of the mnemonic delay is varied, to characterize how response variability increases with the duration of maintenance. To test the model prediction of increased distractibility dependent on target—distractor similarity, a set of trials included a distractor during the delay with a variable distance from the target. Starc et al. (2017) found that results largely followed model predictions, whereby patients exhibited increased variance and less working memory precision as the delay period increased relative to healthy controls. Schizophrenia patients also exhibited increased working memory distractibility, with reports biased toward distractors at specific spatial locations. This study illustrates a productive computational psychiatry approach in which predictions from biophysically based neural circuit models of cognition can be translated into experiments in clinical populations.

1.5.2 Decision Making

Broadly, decision making function is impaired in multiple psychiatric disorders (Lee, 2013). To study dysfunction in neural circuit models, we focus on perceptual decision making in task paradigms similar to those studied via electrophysiology in nonhuman primates. As reviewed above, cortical attractor network models have been developed to capture behavior and neuronal activity from association cortex during random-dot motion paradigms (Wang, 2002; Furman and Wang, 2008). In these two-alternative forced choice tasks, a random-dot motion stimulus is presented, and the subject must report the net direction of motion (e.g., left vs. right). The coherence of the random-dot pattern can be parametrically varied to control the strength of perceptual evidence and thereby task difficulty. The psychometric function, giving the percent correct as a function of coherence, defines the discrimination threshold as the coherence eliciting a certain level of accuracy.

Random-dot motion paradigms have been applied to clinical populations, and have revealed impaired perceptual discrimination in schizophrenia, as measured by a higher discrimination threshold (Chen et al., 2003, 2004, 2005). Similar impairments in the discrimination threshold have also been observed in patients with autism spectrum disorder (Milne et al., 2002; Koldewyn et al., 2010). These impairments are typically interpreted as evidence of neural dysfunction in sensory representations (Butler et al., 2008). However, it is possible that such impairments may have contributions from dysfunction in evidence accumulation downstream from early sensory areas, within association cortical circuits.

To explore this issue, Lam et al. (2017) studied the effects of altered E/I balance in the association cortical circuit model of decision making developed by Wang (2002). E/I ratio was perturbed bidirectionally to compare the impact of elevated versus lowered E/I ratio via NMDA receptor hypofunction on inhibitory versus excitatory neurons, respectively. Interestingly, Lam et al. (2017) found that disruption of E/I balance in either direction can similarly impair decision making as assessed by psychometric performance, following an inverted-U dependence on E/I ratio (Fig. 1.2D). Therefore, the standard psychophysical measurements from clinical populations cannot dissociate among distinct circuit-level alterations: elevated E/I ratio, lowered E/I ratio, or an upstream sensory coding deficit.

Nonetheless, Lam et al. (2017) found that these regimes make dissociable predictions for the time course of evidence accumulation. The random-dot motion task paradigm promotes a cognitive strategy of evidence accumulation across the stimulus presentation. Both in the circuit model and in empirical psychophysical behavior, the choice is not uniformly sensitive to the stimulus value at all time points due to bounded accumulation (Kiani et al., 2008). Multiple more complex task paradigms have been developed to characterize the time course of evidence accumulation. For instance, in the "pulse" task paradigm (Huk and Shadlen, 2005; Wong et al., 2007), a brief pulse of additional coherence is inserted at a variable onset time during the otherwise constant-coherence stimulus (Fig. 1.2E). This pulse induces a shift of the psychometric function according to pulse coherence. The dependence of this shift on pulse onset time reflects the weight of that time point on choice.

The pulse paradigm, as well as other paradigms, was able to dissociate distinct decision making impairments under altered E/I ratio (Fig. 1.2E). Under elevated E/I ratio, decision is impulsive: perceptual evidence presented early in time is weighted much more than late evidence. In contrast, under lowered E/I ratio, decision making is indecisive: evidence integration and winner-take-all competition between options are weakened. These effects are qualitatively captured by modifying a widely used abstract model for decision making from mathematical psychology, the

drift diffusion model (Ratcliff, 1978; Gold and Shadlen, 2007). The standard drift diffusion model assumes perfect integration with an infinite time constant for memory. Lowered E/I ratio in the circuit model can be captured by "leaky" integration with finite time constant for memory. In contrast, elevated E/I ratio can be captured by "unstable" integration, which has an intrinsic tendency to diverge toward the decision threshold. This study demonstrates the potential to link synaptic-level perturbations in neural circuit models to measurable cognitive behavior and to more abstract models from mathematical psychology.
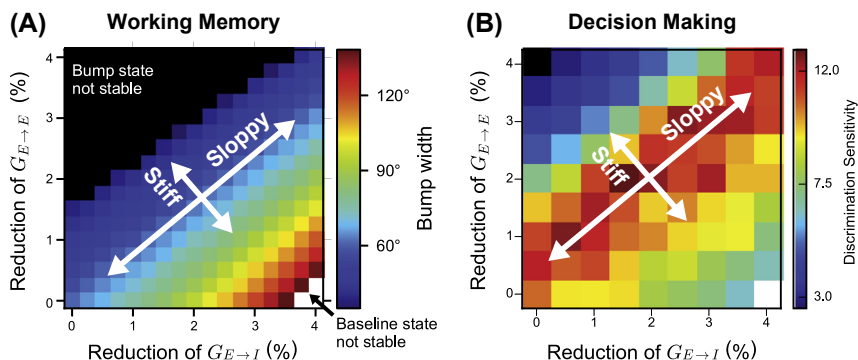
1.6 CRITICAL ROLE OF EXCITATION−INHIBITION BALANCE IN COGNITIVE FUNCTION

As described in the above section, neural circuit models of cognitive functions can generate dissociable predictions for how distinct synaptic perturbations impact behavior under various task paradigms. Biophysically based models can also suggest what aspects of neural activity or behavior may be differentially sensitive or robust to particular manipulations by pathology, compensation, or treatment. Changes in certain network parameters, or the combinations of parameters, may have much stronger impact on model behavior than do changes in other parameter combinations. A "sloppy" axis in parameter space is one among which the model response is relatively insensitive to perturbations in that parameter combination, whereas a "stiff" axis is one in which the model response is highly sensitive to perturbations (Gutenkunst et al., 2007).

Murray et al. (2014) and Lam et al. (2017) characterized function in theses neural circuit models under parametric variation in E/I ratio. Specifically, they explored the parameter space of reductions of NMDA receptor conductance onto both inhibitory interneurons (elevating E/I ratio) and onto excitatory pyramidal neurons (reducing E/I ratio) (Fig. 1.3). For the working memory model, circuit function is determined by the width of the mnemonic persistent activity pattern. For the decision making model, circuit function can be measured through discrimination sensitivity (inverse of the discrimination threshold). Similarly for both circuit models for working memory and decision making, E/I ratio was found to be a key parameter for optimal network function. Following relatively small perturbations, circuit function is robust as long as E/I balance is preserved. Preserved E/I ratio therefore corresponds to a "sloppy" axis in this parameter space. In contrast, even subtle changes to E/I ratio (along a "stiff" axis) have a strong impact on model function.

If the imbalance is substantial, either elevated or lowered, the circuit can lose multistability. If disinhibition is too strong (via elevated E/I

ratio), then the spontaneous state is no longer stable. Conversely, if recurrent excitation is too weak (via lowered E/I ratio), then the circuit cannot support persistent activity. Collectively, these analyses reveal that E/I balance is vital for optimal cognitive performance in these cortical circuit models. This suggests that despite the complexity of synaptic alterations in disorders such as schizophrenia, the impact on cognitive function in neural circuits may be understandable in terms of their "net

FIGURE 1.3 Dependence of circuit function on synaptic parameters: a critical role of excitation—inhibition (E/I) balance in both working memory and decision making. The plots illustrate a parameter space of reductions of two recurrent NMDAR conductance strengths from excitatory pyramidal neurons: onto inhibitory interneurons ($G_{E\rightarrow I}$) or onto excitatory pyramidal neurons ($G_{E\rightarrow E}$). This analysis characterizes the sensitivity of model function to joint perturbations of these two parameters. (A) For the working memory circuit, we measured the width of the working memory bump attractor state. Bump width affects mnemonic precision and distractibility during working memory maintenance. (B) For the decision making circuit, we measured the discrimination sensitivity, which is defined as the inverse of the discrimination threshold (i.e., coherence which yields 81.6% correct). A higher sensitivity corresponds to better performance. For both working memory and decision making circuits, within this range of perturbation, if $G_{E\rightarrow I}$ and $G_{E\rightarrow E}$ are reduced together in a certain proportion, circuit performance is essentially unaltered, because E/I balance is maintained. E/I balance defines a "sloppy" axis in parameter space along which the function is insensitive. In contrast, the function is highly sensitive to small orthogonal perturbations, along a "stiff" axis (Gutenkunst et al., 2007). Reduction of $G_{E\rightarrow I}$ in greater proportion elevates E/I ratio and can degrade performance: for working memory, due to broadened mnemonic representations; for decision making, due to highly unstable integration leading to impulsive selection. In contrast, reduction of $G_{E\rightarrow E}$ in greater proportion lowers E/I ratio and can degrades performance: for working memory, due to loss of the bump attractor state; for decision making, due to indecisive selection. These findings indicate that E/I ratio is a crucial effective parameter for cognitive function in these circuits, with an "inverted-U" dependence of function on E/I ratio. *Panels (A and B) adapted from Murray, J.D., Anticevic, A., Gancsos, M., Ichinose, M., Corlett, P.R., Krystal, J.H., Wang, X.-J., 2014. Linking microcircuit dysfunction to cognitive impairment: effects of disinhibition associated with schizophrenia in a cortical working memory model. Cereb. Cortex 24, 859—872; Lam, N.H., Borduqui, T., Hallak, J., Roque, A.C., Anticevic, A., Krystal, J.H., Wang, X.-J., Murray, J.D., 2017. Effects of altered excitation-inhibition balance on decision making in a cortical circuit model. bioRxiv. http://dx.doi.org/10.1101/100347, respectively.*

effect" on effective parameters, such as E/I ratio, to which the circuit is preferentially sensitive.

1.7 FUTURE DIRECTIONS IN NEURAL CIRCUIT MODELING OF COGNITIVE FUNCTION

In this chapter, we have primarily reviewed studies leveraging biophysically based neural circuit models to explore the effects of altered E/I balance on the core cognitive functions of working memory and decision making. These studies revealed that E/I ratio is a critical property for proper cognitive function in cortical circuits. Furthermore, they provide a test bed for computational psychiatry demonstrating that neural circuit models can play a translational role between basic neurophysiology and clinical applications. Here we turn to some critical areas for future modeling to address.

1.7.1 Integrating Cognitive Function With Neurophysiological Biomarkers

As noted above, biophysically based circuit models are well positioned to explore the mechanisms through which synaptic-level perturbations may be associated with neurodynamical biomarkers. In the context of schizophrenia, circuit models have been applied to studying mechanisms of disrupted gamma-band oscillations (Vierling-Claassen et al., 2008; Spencer, 2009; Volman et al., 2011; Rotaru et al., 2011), which can be related to EEG/MEG data from patients (Uhlhaas and Singer, 2010). At very different spatiotemporal scales, circuit models of large-scale "dysconnectivity" can be related to resting-state BOLD data (Yang et al., 2014, 2016a). Such biomarker-related models are mostly nonfunctional, in the sense that they do not directly relate to cognitive function or behavior. Future modeling work is needed in the integration of cognitive function with neurophysiological biomarkers across multiple scales of analysis.

1.7.2 Incorporating Further Neurobiological Detail

To address increasingly complex and detailed questions about neural circuit dysfunction, future models will need to incorporate further elements of known neurobiologically which can be constrained and tested with experiments. One notable limitation is that the cortical circuit models described above only contain a single type of inhibitory interneuron, and therefore are not able to speak to important questions regarding preferential dysfunction in specific interneuron cell types. There are key differences between parvalbumin-expressing and somatostatin-expressing

interneurons, which differ in their synaptic connectivity and functional responses (Gonzalez-Burgos and Lewis, 2008). Microcircuit models that propose a division of labor among interneuron classes (Wang et al., 2004; Yang et al., 2016b) have the potential to make dissociable predictions for dysfunction in distinct cell types. Another aspect of microcircuitry for model extension is laminar structure in cortex (Mejias et al., 2016), which may address to mechanistic hypotheses of impaired predictive coding (Bastos et al., 2012). Beyond the level of local microcircuitry, further modeling work is needed on distributed cognitive computations across brain areas (Chaudhuri et al., 2015; Murray et al., 2017), and their application to alterations in large-scale network dynamics in psychiatric disorders (Yang et al., 2014, 2016a).

1.7.3 Informing Task Designs

These modeling studies suggest important considerations for the design of cognitive tasks applied to computational psychiatry. In each model, multiple modes of cortical dysfunction (e.g., elevated vs. lowered E/I ratio vs. upstream sensory coding deficit) can impair performance. Standard performance analyses in common task paradigms (e.g., match−nonmatch error rate in working memory, or psychometric threshold in decision making) may be insufficient to resolve dissociable predictions. More fine-grained analyses of task behavior should distinguish different types of errors or deficits, rather than simply measuring overall performance, which could be impaired due to deficits in distinct cognitive subprocesses (e.g., encoding vs. maintenance for working memory) or opposing deficits in a single subprocess (e.g., leaky vs. unstable integration in decision making). Circuit modeling can provide insight into the variety of potential "failure modes" in a cognitive function, and into which task designs can reveal them. In turn, alignment of a task design with a circuit model allows for generation of mechanistic neurophysiological hypotheses from behavioral measurements.

1.7.4 Studying Compensations and Treatments

Finally, of utmost relevance to psychiatry, biophysically based circuit modeling has the potential to provide a method for simulating possible effects of treatments (or compensations), which act at level of ion channels and receptors. As a proof-of-principle example of this, Murray et al. (2014) examined in the working memory circuit model how E/I balance can be restored through compensations acting on multiple parameters; for instance, elevated E/I ratio due to disinhibition can be compensated for by a treatment that strengthens inhibition or by one that attenuates excitation. In turn, restoration of E/I balance ameliorated the associated

deficits in working memory behavior. However, further development and refinement of biophysically based models is needed to go beyond proof of principle. Future development in this area will benefit from the other directions noted above. Incorporation of more detailed microcircuitry and receptors will be needed to better capture pharmacological effects. Integration of biomarkers and behavior in the models will allow refinement through more direct testing with empirical data from pharmacological manipulations in animal models and humans. Future studies in this area hold exciting promise of contributing to the rational development of treatments in psychiatry, grounded in basic neuroscience.

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