Toward a Prefrontal Microcircuit Model for Cognitive Deficits in Schizophrenia

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I present here a biophysically-based model of cortical microcircuits capable of both internal representation (memory storage) and dynamical processing (decision and action selection). The model is illustrated through computer simulations that account for neurophysiological and behavioral data from studies using nonhuman primates. This computational theory proposes that an interplay between slow reverberating excitation and competitive synaptic inhibition enables a cortical area, such as the prefrontal cortex, to subserve cognitive functions. It is argued that quantitatively accurate microcircuit models can potentially provide a framework for a systematic approach to pharmacological treatment of schizophrenia and other mental disorders.

Introduction

Among core features of schizophrenia are deficits in cognitive functions, such as working memory, decision making and inhibitory control. Converging evidence indicates that these impairments are associated with abnormal function of the prefrontal cortex (PFC) [27,73,65]. Last 10 years have witnessed great strides in basic research of PFC, galvanized by a cross-disciplinary approach combining physiology of behaving animals, human functional brain imaging, anatomical and biophysical analysis of neural circuitry, computational modeling [65,50,71]. Information is accumulating at rapid pace concerning the structure and dynamical operation of PFC in normal subjects. Knowledge thus gained is beginning to shed insights into the cellular and circuit basis of PFC dysfunction associated with schizophrenia.

In this endeavour, computational models are playing an increasingly significant role. For example, a cardinal prefrontal function is working memory, and physiological studies of alert nonhuman primates have revealed mnemonic 'persistent activity' in PFC, at the single cell level, during working memory [22,20,51,55,59]. An open question is how to link neural processes observed in behaving animals with the underlying cellular mechanisms; Realistic neural network modeling has proven to be a valuable tool in this regard, helping bridge the gaps between levels of investigation that would be difficult to achieve with existing experimental methods. Biophysically-based microcircuit models have become possible only recently, thanks to advances in our knowledge of the biophysics of single neurons [40,44] and synapses [46,1], as well as microcircuit connectivity of neocortex [63,17].

Interests in a computational approach also stem from the fact that cognitive functions involve strongly recurrent cortical circuits with an abundance of feedback loops, the behaviors of which are not easy to predict by intuition alone. Indeed, a central tenet of the field is the concept of reverberation, or recurrent dynamics in a neural circuit [42,30,4,68]. Broadly speaking, feedback mechanisms underlying reverberation can either arise from recurrent network dynamics [5,39,67,18,10,62,7,52], or from intrinsic membrane/intracellular dynamics of single cells [8,19,33,41,25,45]. The idea of reverberation is made precise mathematically, in terms of 'dynamical attractors' [74,3,4,68]. The mathematical term 'attractor' simply means any self-sustained and stable state of a dynamical system, such as a neural network. According to this picture, in a working memory system, the spontaneous (resting) state and stimulus-selective memory states are assumed to represent multiple attractors, such that a

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memory state can be switched on and off by transient inputs. The challenge today is to test whether the attractor theory is suitable for describing cortical processes of cognition and, if so, to find out how attractor dynamics can be instantiated by neuronal hardware in the brain.

A biophysically-based model of working memory

Arguably the simplest paradigm for studying prefrontal function is delayed response tasks [32], in which the sensory stimulus and motor response are separated by a brief delay period, during which time the sensory information must be actively held in mind by the subject. An especially elegant experimental design is the spatial delayed oculomotor response task (Fig. **1**A). Using this task, Funahashi et al. [20] found that many neurons in the dorsolateral prefrontal cortex including and surrounding the principal sulcus, and in the frontal eye field, exhibited mnemonic persistent activity during the delay period (Fig. **1**B). Remarkably, the delay activity of a recorded neuron was selective for preferred spatial cues (the cell's 'memory field'), and this selectivity could be quantified by a bell-shaped tuning curve (Fig. **1**C). Thus, the question of prefrontal microcircuitry underlying working memory could be formulated in cellular and synaptic terms [28,68,14]: what are the excitatory-inhibitory synaptic mechanisms for the formation of memory fields? what are the microcircuitry properties of the prefrontal cortex, such as local horizontal connections, that generate persistent activity? We have investigated these questions using a biophysically constrained model of recurrent cortical microcircuit [8,10,66,58].

A network model for the Funahashi experiment of spatial working memory is illustrated in Fig. **2**A. The key feature is the preeminence of recurrent connections ('loops') between neurons via 'horizontal' connections [37,34]. A commonly assumed network architecture is the so called 'Mexican-hat': localized recurrent excitation between pyramidal cells with similar preference to spatial cues, and broader inhibition mediated by interneurons. Models of synapses and single cells are calibrated quantitatively by cortical electrophysiological studies. Fig. **2**B shows a model simulation of the delayed oculomotor task [10,57] (for movie presentation of this model, go to http://wanglab.ccs.brandeis.edu/). Initially, the network is in a resting state in which all cells fire spontaneously at low rates. A transient input (in this case at 180 degrees) drives a subpopulation of cells to fire at high rates. As a result they send recruited excitation to each other via horizontal connections. This internal excitation is large enough to sustain elevated activity, so that the firing pattern persists after the stimulus is withdrawn. Synaptic inhibition ensures that the activity does not spread to the rest of the network, and persistent activity has a bell shape ('bump attractor'). At the end of a mnemonic delay period the cue information can be retrieved by reading out the peak location of the persistent activity pattern; and the network is reset back to the resting state. In different trials, a cue can be presented at different locations. For example, across eight cue presentations the firing activity of a single cell (Fig. **2**C) can be compared with the single-unit recording data from monkey's prefrontal cortex [20]. At the network level, each cue triggers a persistent firing pattern of the same bell-shape but peaked at a different location. A spatial working memory network thus requires a continuous family of 'bump attractors', each encoding a potential location [8,10,57,72].

Thus, this biologically constrained model captures salient experimental observations from behaving monkeys. What have we learned from such a model? An important lesson is that multiple aspects of network function can be traced to a few key circuit features. Namely, we found a complementarity of two requirements. On the one hand, to ensure stable working memory behavior, reverberatory neurodynamics should be strong but instantiated by a slow positive feedback mechanism, such as synaptic excitation mediated by the NMDA receptors [67,68,66]. On the other hand, it is essential that exuberant excitation be tightly balanced by inhibition [10,7,72]. The balance between strong excitation and inhibition underlies the generation of persistent activity and its selectivity to sensory stimuli [10,72]. The model predicts quantitative features of GABAergic inhibitory cells [10,72], which have been supported by direct measurements of putative inhibitory neurons from behaving monkeys during working memory [12] (Fig. **1**, bottom panel), and by the observation that GABAA receptor antagonists resulted in the loss of spatial tuning of prefrontal neurons during a delayed oculomotor task [56]. Moreover, balanced excitation and inhibition naturally gives rise to coherent network oscillations, typically in the gamma (40 Hz) frequency range [67,10,66,58] (Fig. **3**). Therefore, fast rhythms, that are commonly observed in awake behaving animals, may be a characteristic sign of the engagement of strongly reverberatory cortical circuits in cognition and memory.

A key aspect of memory maintenance is the brain's ability to filter out irrelevant sensory stimuli. In delayed response experiments using intervening stimuli (distractors), mnemonic activity has been shown to be easily disrupted by distractors in inferotemporal neurons but not in prefrontal neurons [51]. Similarly, delay period activity in posterior parietal cortex appears to be sensitive to distractors [54,13]. We found that synaptic inhibition provides a candidate mechanism enabling our model network to resist distracting stimuli during working memory [10,7]. Interestingly, the network's ability to ignore distractors is sensitive to modulation by dopamine of recurrent excitation and inhibition (Fig. **4**) [7,18]. Therefore, even a mild impairment of dopaminergic signaling in prefrontal cortex could be dramatically detrimental to robust working memory maintenance in spite of ongoing sensory flow.

It is worth noting that, although these types of models were designed for working memory, it turns out that they can account for decision making processes as well [69,43,53]. Slow reverberation can serve time integration of information, and inhibition gives rise to winner-take-all competition, both computations being of central importance to decision making. In this way, our model brings together two contrasting views about prefrontal function, maintenance of internal representation versus cognitive processes [16,50,75], into an unifying theoretical framework.

Distinct features of prefrontal microcircuit and implications for schizophrenia

Quantitative differences breed qualitatively different behaviors. That a cortical area exhibits a new type of behavior does not nec-

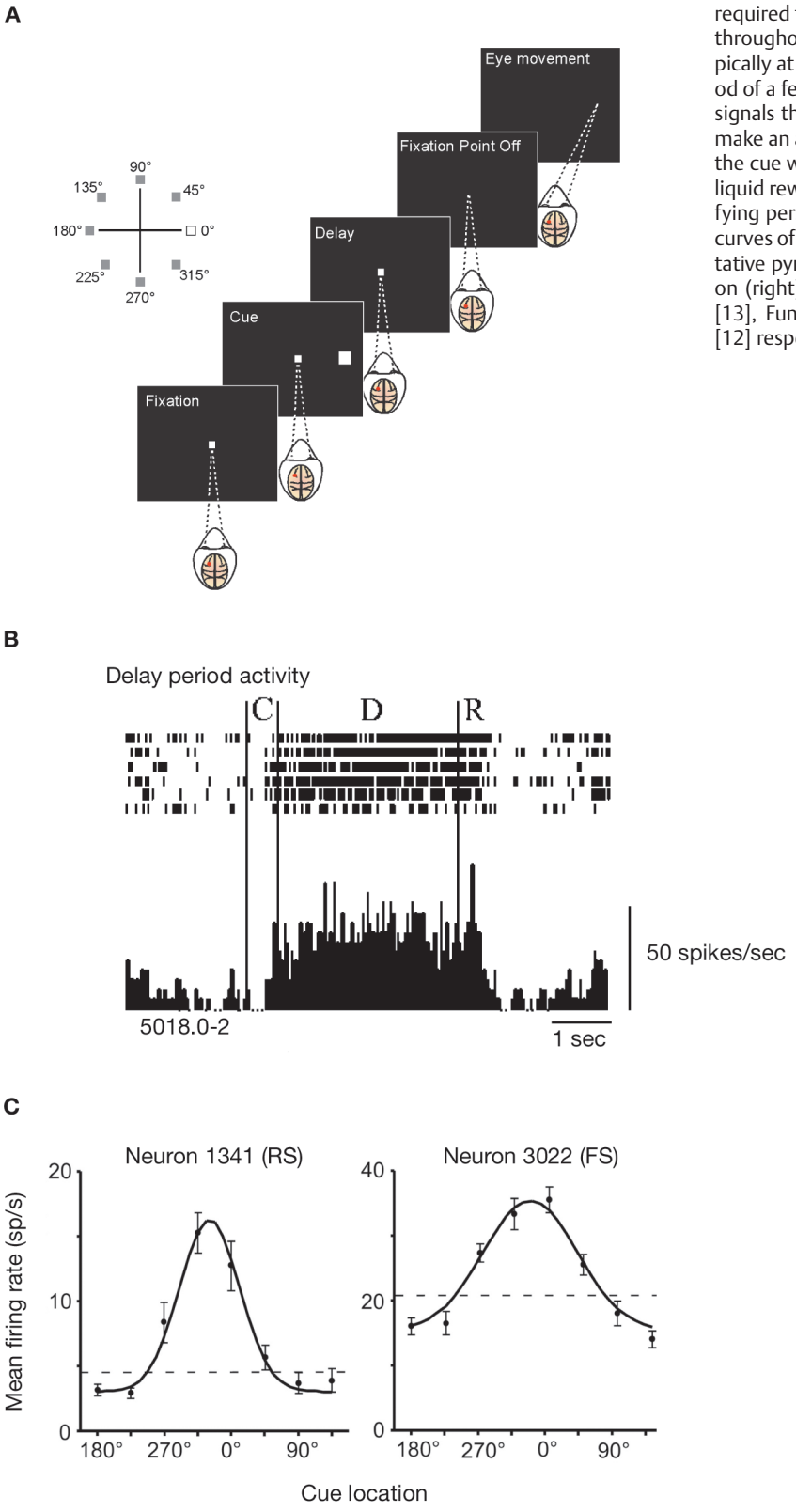

Fig. **1** (A) Oculomotor delayed response task. The monkey is required to foveate at a fixation point at the center of the screen throughout the trial. A spatial cue is subsequently presented, typically at one of eight locations (inset at left). After a delay period of a few seconds, the disappearance of the fixation light spot signals the end of the delay. At that moment the monkey must make an accurate saccadic eye movement to the location where the cue was shown before the delay period, in order to collect a liquid reward. (B) Activity of a single prefrontal neuron, exemplifying persistent discharges during working memory. (C) Tuning curves of mnemonic delay period activity in a regular spiking putative pyramidal cell (left) and a fast-spiking putative interneuron (right). (A – C) are adopted from Constantinidis and Procyk [13], Funahashi et al. [20], Constantinidis and Goldman-Rakic [12] respectively, with permission.

essarily mean that the circuit must possess unique biological machineries completely different from other areas. Hence, persistent activity may be generated in the prefrontal cortex when the strength of recurrent excitation (mediated by AMPA+NMDA receptors combined) exceeds a critical threshold, whereas this may not be the case for a sensory area such as the primary visual cortex. Based on our modeling results, we can extend this idea and propose that, for stable function of a working memory circuit, the NMDA/AMPA ratio at recurrent synapses should also be above a critical level. This result is especially relevant to schizophrenia research, in light of the mounting evidence that NMDA hypofunction underlies certain cognitive deficits in schizophrenia [15]. Interestingly, immunochemical analysis revealed a significantly larger amount of mRNA expression of NMDA re-

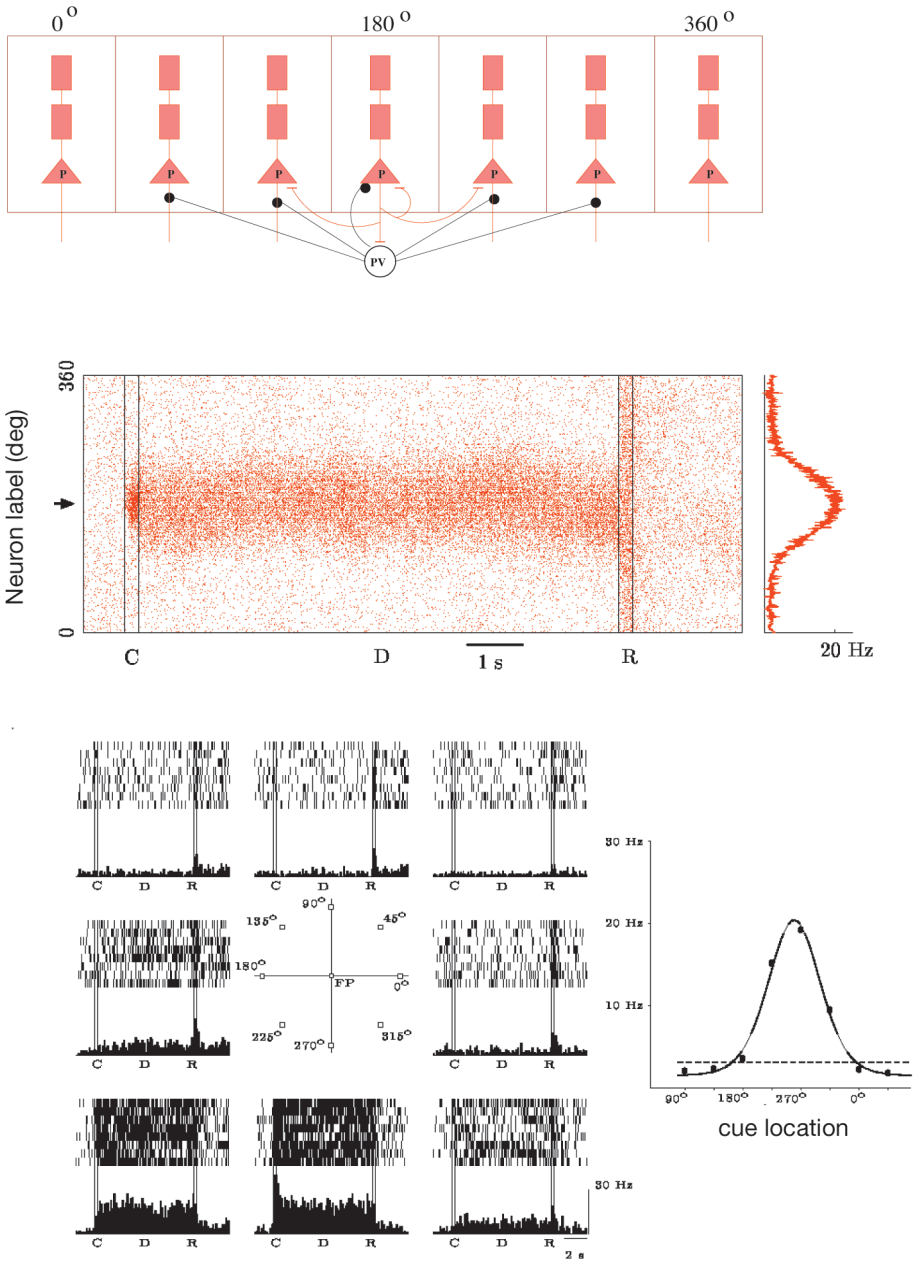

Fig. **2** Working memory maintained by a spatially tuned network activity pattern (a "bump attractor"). Top: model architecture. Excitatory pyramidal cells are labeled by their preferred locational cues (0 to 360 degree). Pyramidal cells of similar preferred cues are connected through local E-to-E connections. Interneurons receive inputs from excitatory cells and send feedback inhibition by broad projections. Middle: a network simulation of delayed oculomotor response experiment. C: cue period D: delay period, R: response period. Pyramidal neurons are labeled along the y-axis according to their preferred cues. The x axis represents time. A dot in the rastergram indicates a spike of a neuron whose preferred location is at y, at time x. Note the enhanced and localized neural activity that is triggered by a transient cue stimulus and persists during the delay period. The population firing profile, averaged over the delay period, is shown on the right. Bottom Left: Firing activities of a single cell when the cue was shown in one of the 8 locations indicated in the center diagram. This neuron exhibits an elevated persistent activity in the delay only for one direction (270 degrees), and is suppressed relative to inter-trial spontaneous activity in the upper visual field. Bottom Right: the delay period tuning curve shows the average discharge rate during the delay period (circles), together with a Gaussian fit of the data. The horizontal line indicates average inter trial spontaneous activity. Data provided by A. Compte.

ceptor subunits in prefrontal neurons, compared to primary visual cortical neurons (Fig. **5**) [66]. Moreover, NMDA subunit mRNA expressions are abnormal in PFC of schizophrenics [2]. Traditionally, the function of NMDA conductance is almost exclusively emphasized in terms of its role in long-term synaptic potentiation and depression. Our model presents an alternative view, namely NMDA receptors directly mediate slow excitatory synaptic transmission that critically contributes to working memory and decision making. If proven experimentally, this model would provide a mechanistic basis for the NMDA hypofunction hypothesis of schizophrenia; and it would explain why NMDA receptor antagonists produce working memory impairment in healthy human subjects, similar to that seen in schizophrenia [35].

On the other side of a balancing act, prefrontal cortex is also likely to be endowed with specialized inhibitory circuitry, composed of multiple cell subtypes (see Markram et al. [47] for a review). For example, the distributions of three major subtypes of GABAergic cells (expressing parvalbumin, calbindin and calretinin, respectively) appears to be quite different in macaque monkey prefrontal cortex (Fig. **6**B) [11,23] compared to primary visual cortex [6,48]. To explore differential roles of different interneuron subtypes, we have extended our model of spatial working memory to incorporate three subclasses of interneurons classified according to their synaptic targets [72]. In this model (Fig. **6**A), in addition to widespread inhibition mediated by perisoma-targeting and parvalbumin-containing (PV) interneurons, dendrite-targeting (calbindin-containing, CB) interneurons receive inputs from interneuron-targeting (calretinin-containing, CR) interneurons, leading to an activity-dependent local disinhibition of pyramidal cells. We found that the disinhibition mechanism, mediated by CR inhibition of CB interneurons, contributes significantly to the formation of memory field, as well as the network's ability to filter out distracting stimuli [72].

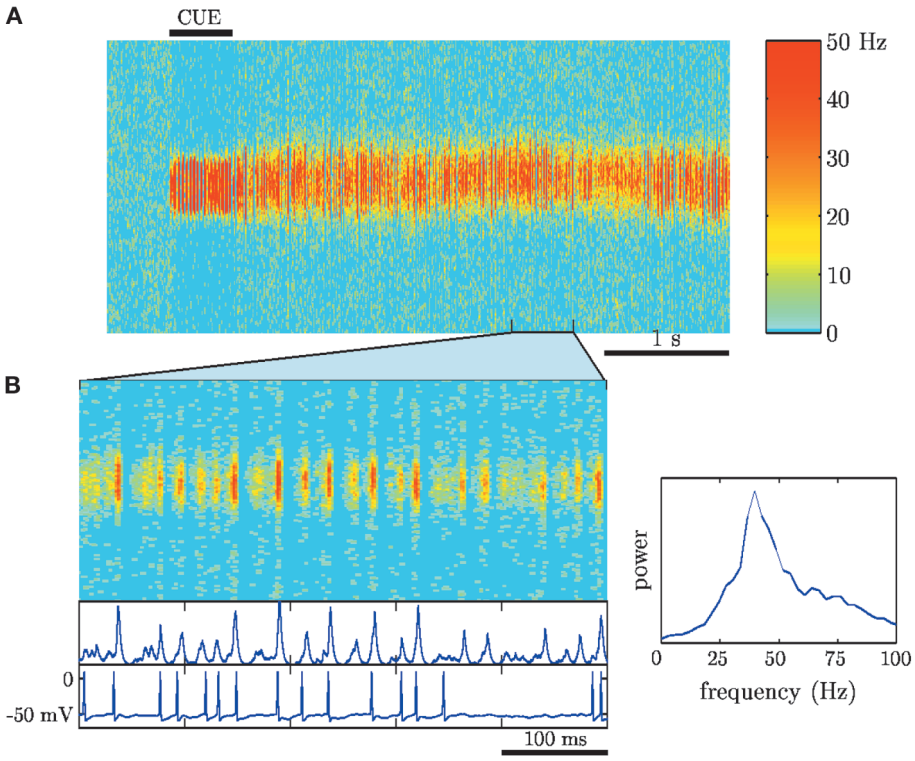

Fig. **3** Gamma oscillations during working memory, (A) Spatiotemporal firing pattern of a spatial working memory model same as in Fig. 2 (with slightly different parameters) except that firing rates are color-coded. (B) 500 ms blowup of (A) to show synchronous oscillations in the spatiotemporal activity pattern (top), the local field potential (middle) and membrane potential of a single neuron (bottom). On the right is shown the power spectrum of the local field, demonstrating a large peak at about 40 Hz. Adopted from Compte et al. [10] with permission.

These results have functional implications for the observed pathology of inhibitory circuits associated with schizophrenia [38]. The model describes quantitatively the network parameters that control (40 Hz) oscillations, thus could be used to establish a precise link between abnormal features of rhythm [64,36] and its underlying cellular substrates. Furthermore, the model points to an explanation of how a reduced excitation and inhibition leads to PFC's deficient ability to filter out distracting stimuli, similar to enhanced distractibility observed in schizophrenic patients [21,26,49].

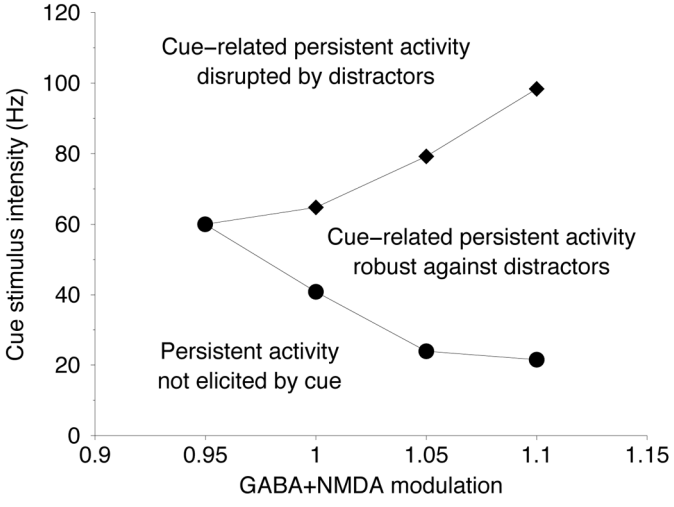

Fig. **4** Resistance against distractors. Behavior of an object working memory model is shown as a function of dopamine modulation of NMDAR mediated recurrent excitation and GABAAR inhibition (x-axis) and amplitude of cue stimulation (y-axis). A very weak stimulus (initial cue) cannot elicit persistent activity (lower left region), whereas a strong stimulus (distractor) can override recurrent dynamics and disrupt delay activity (upper left region). The desirable behavior (robust persistent activity in spite of distractors) (middle right region) is sensitive to dopamine modulations. Adopted from Brunel and Wang [7] with permission.

Concluding remarks

Computational modeling, in close interplay with laboratory experiments, offers a promising approach to synthesize the staggering amount of data, uncover general principles, and help identify cellular and network mechanisms. Microcircuitry is at a level of complexity ideally suited for linking cognitive network functions and the underlying biophysical substrates; thus ultimately for elucidating how a psychiatric drug really works. An example par excellence is dopamine, whose actions range from its bidirectional interaction with NMDA receptor [9,31], targeting various ion channels in single cells [61], to modulation of the ratio of dendritic versus somatic inhibition of pyramidal neurons [24]. A systematic and rational understanding of dopamine modulation would seem impossible, unless we have a quantitative model within which to examine these disparate (some excitatory, others inhibitory) effects in the context of the delicate balancing act of excitation and inhibition, at the heart of strongly nonlinear dynamics that underlies cognitive processes in prefrontal cortex. In this sense, microcircuit neurodynamics holds the key to a theoretical foundation for neuropharmacology and molecular psychiatry [29].

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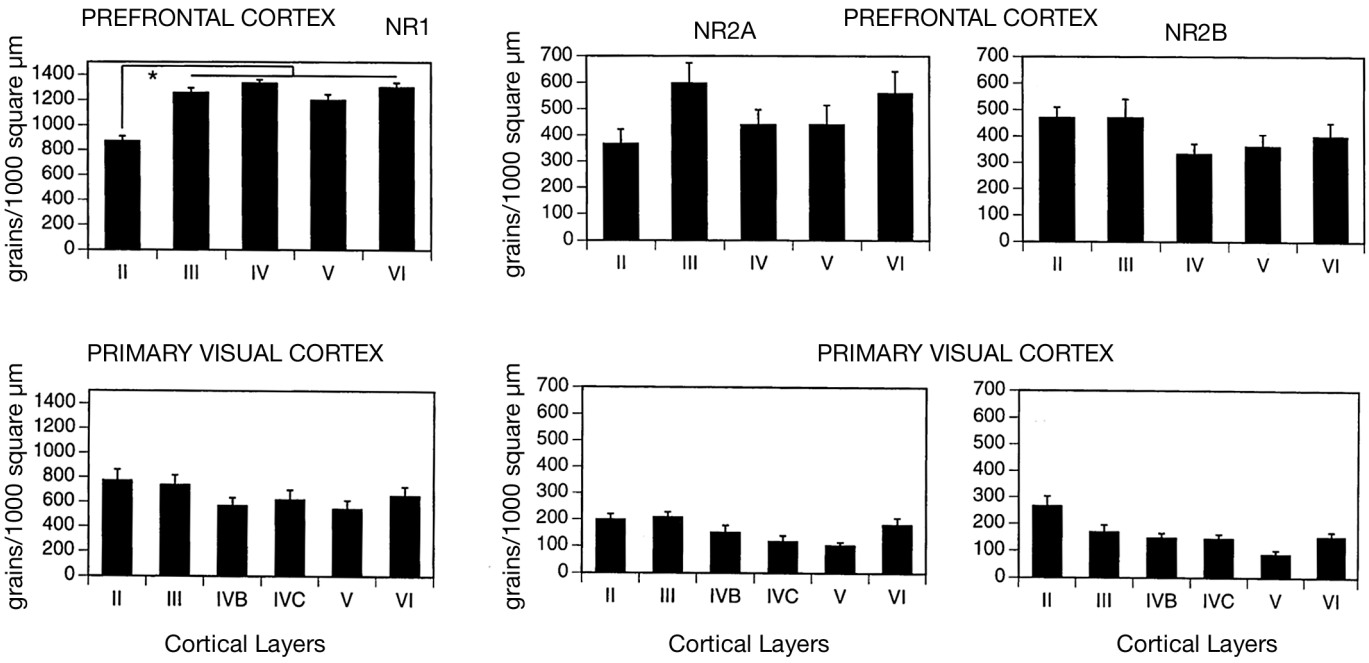

Fig. **5** mRNA expression of NMDA receptor subunits NR1, NR2A and NR2B in human prefrontal cortex (top) and primary visual cortex (bottom). Adopted from Scherzer et al. [60] with permission.

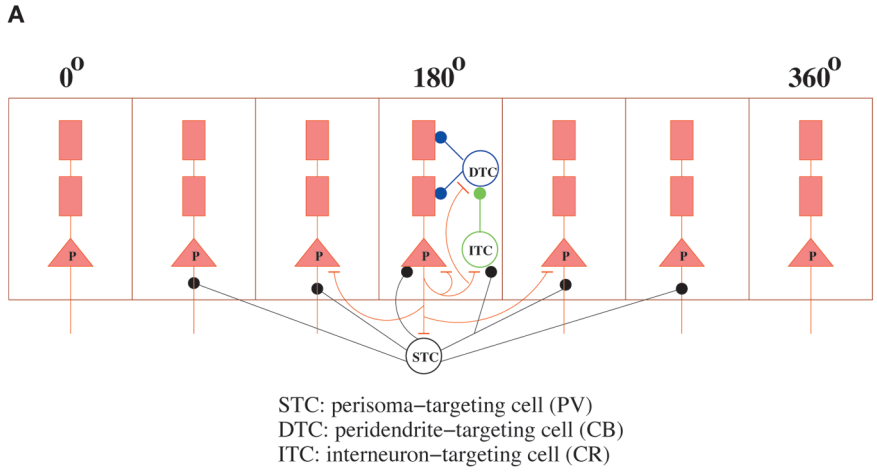

Fig. **6** (A) A spatial working memory model with three subclasses of GABAergic interneurons. Pyramidal (P) neurons are arranged according to their preferred cues (0 to 360 degrees). There are localized recurrent excitatory connections, and broad inhibitory projections from perisoma-targeting (parvalbumin-containing, PV) fast-spiking neurons to P cells. Within a column, Calbindin-containing (CB) interneurons target the dendrites of P neurons, whereas calretinin-containing (CR) interneurons preferentially project to CB cells. Excitation of a group of pyramidal cells recruits locally CR neurons, which sends enhanced inhibition to CB neurons, leading to dendritic disinhibition of the same pyramidal cells. Adopted from Wang et al. [72] with permission. (B) Proportional distribution of PV, CB and CR expressing GABAergic cells in three subregions of the prefrontal cortex of the macaque monkey. Data taken from Conde et al. [11] with permission.

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