



Towards biologically constrained attractor models of schizophrenia

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Abstract

Alterations in neuromodulation or synaptic transmission in biophysical attractor network models, as proposed by the dominant dopaminergic and glutamatergic theories of schizophrenia, successfully mimic working memory (WM) deficits in people with schizophrenia (PSZ). Yet, multiple, often opposing alterations in memory circuits can lead to the same behavioral patterns in these network models. Here, we critically revise the computational and experimental literature that links NMDAR hypofunction to WM precision loss in PSZ. We show in network simulations that currently available experimental evidence cannot set apart competing biophysical accounts. Critical points to resolve are the effects of increases vs. decreases in E/I ratio (e.g. through NMDAR blockade) on firing rate tuning and shared noise modulations and possible concomitant deficits in short-term plasticity. We argue that these concerted experimental and computational efforts will lead to a better understanding of the neurobiology underlying cognitive deficits in PSZ.

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Abbreviations

WM, working memory; PSZ, people with schizophrenia; NMDA, N-methyl-D-aspartic acid; NMDAR, NMDA receptor; STP, short-term plasticity.

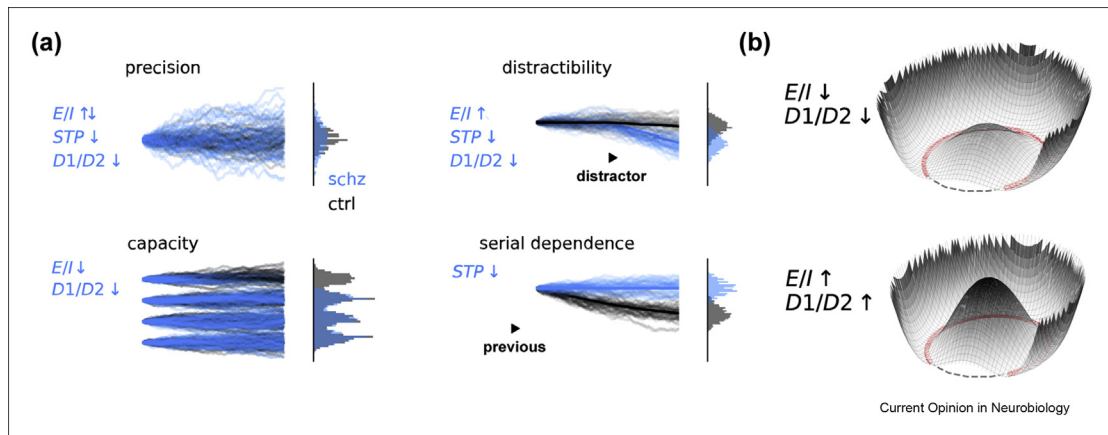
As part of the new field of computational psychiatry, computational models have been increasingly used to link molecular and cellular mechanisms with systemic

and behavioral alterations in psychiatric diseases [1–3]. Dynamical network accounts of brain disease reach from models of distributed processing across brain areas to biophysical models of the local cortical circuitry [4,5]. Computational models contribute quantitative perspectives and mechanistic hypotheses about pathological brain functions that have a transformative potential on psychiatric research [6]. However, advancing toward valid model-based links between mechanisms and symptoms will require a concerted effort of theoretical and neurophysiological research to select among currently underconstrained computational models. We illustrate this point here by focusing on circuit models of association cortices that reproduce working memory (WM) alterations in people with schizophrenia (PSZ) (Figure 1a and Box 1; for a comprehensive review on computational models of schizophrenia, see Refs. [1–3,7]). These specific models have attracted attention for combining rich quantitative descriptions of multiple behavioral deficits in PSZ with detailed, biologically plausible mechanisms (Box 1), informed by neurophysiological data from behaving animals [8–11] and *in vitro* experiments [12,13]. Briefly, WM in these circuit models is held in patterns of sustained, stimulus-specific network activity. While discrete WM tasks (e.g. two-alternative forced choice tasks) are typically modeled through interconnected stimulus-selective subpopulations, continuous tasks (e.g. the oculomotor delayed response task) are encoded by a continuous, ring-shaped network of tuned neurons that produce localized bumps of sustained neural activity during the mnemonic period.

Attractor stability as a general framework in computational psychiatry

On the basis of these computational models, it has been argued that psychiatric symptoms, and especially those occurring in PSZ, may be more naturally mapped to distortions of network dynamics rather than directly to specific cellular or molecular mechanisms [9,15,16]. In the context of WM, behaviorally relevant changes in network dynamics are chiefly linked to the stability of mnemonic *attractor states*, i.e. stable patterns of sustained network activity that represent memoranda. In this framework, different altered neurobiological mechanisms convergently affect the stability of attractor states (Figure 1b) and determine changes in network

Figure 1



Proposed biophysical mechanisms of schizophrenia and their effect on attractor models of WM. **(a)** Four different quantifiable alterations in spatial WM in PSZ (black: control simulations; blue: schizophrenia (schz) simulations), with an indication of biophysical network mechanisms that have been proposed to underlie them in computational models (Box 1). In all panels, each line represents the parametric value (y-axis, e.g. angular location) of a single memory, held in the format of a localized activity bump through the course of a single trial. Histograms represent the distribution of network readouts. ↑: increase; ↓: decrease; E/I: excitation-inhibition ratio, typically modeled through NMDAR hypofunction at pyramidal cells (E/I ↓) or at inhibitory interneurons (E/I ↑), but other receptor manipulations could similarly affect network dynamics (e.g. GABA_AR dysfunction); STP: short-term plasticity; D1/D2: relative D1-vs. D2-receptor contributions in the dopaminergic system. **(b)** Schematics of a possible energy landscape in continuous ring attractor models. In these models, the deepening or shallowing of attractors is not the only factor that determines the effects of noise, which acts on an orthogonal space (red manifold) [14]. Different angular positions on this low-dimensional manifold encode different stimulus values.

output consistent with disease symptoms (e.g. weaker memories or higher distractibility, Box 1). Dynamical systems models of WM alterations in PSZ have proposed that the flattening of the attractor landscape would lead to less stable memories, lower WM capacity, and increased distractibility [15,17–19]. Detailed biophysical models have shown how this change in network dynamics, consistent with the symptoms of PSZ, can be attained through different mechanistic alterations: from synaptic receptor modulations that alter the excitation-to-inhibition ratio (E/I ratio) of the network [20], over complex neuromodulatory actions of the dopamine system on synaptic and cellular channels [21], to the effect of serotonergic receptors on the excitability of network neurons [22] (Box 1 for more references). In turn, a given alteration of network dynamics may be mitigated by ‘treatment’ manipulations unrelated to the initial mechanistic deficit.

The specific mapping of a given mechanistic alteration (e.g. depleting NMDA receptors (NMDARs)) and the resulting network dynamics effect (e.g. weaker attractor states) may in some cases be difficult to establish. In great part, this is due to our currently limited knowledge about the neurophysiology of the implicated cortical circuits and the still insufficient understanding of biological network models. We illustrate this point in the following by focusing on the lower precision of spatial WM reports in PSZ (Box 1) and how this may be explained by a reduction in glutamatergic NMDAR efficacy or in short-term plasticity (STP), which, in turn,

lead to reduced stability of attractors in the face of random fluctuations. Current computational models establish an ambiguous correspondence between this behavioral phenomenon and NMDAR-mediated changes in E/I ratio: depending on the modeler’s choice among biologically plausible yet distinct model architectures, either increases or decreases in cortical E/I ratio could reduce attractor stability. We suggest that further neurophysiological data is needed to clarify this ambiguity.

E/I ratio has ambiguous effects on WM stability, depending on network biophysics

Experimental evidence for an increased vs. decreased E/I ratio in PSZ is ambiguous: while most evidence points to an increased cortical E/I ratio in PSZ [23–25], possibly caused by hypofunctional NMDARs in inhibitory interneurons (i.e. cortical disinhibition) [12,26–28], other studies have questioned the predominance of inhibitory dysfunction [29] or provided evidence for reduced synaptic spine densities in prefrontal pyramidal cells of PSZ [30,31], suggesting deficits in recurrent excitatory circuitry in PFC. In support of the former hypothesis, computational models that implement cortical disinhibition in WM circuits can explain reduced WM precision and increased distractibility [20,32,33] (but note similar modeling work that instead explains altered decision-making biases under ketamine with a deficit in cortical excitation, rather than a deficit in inhibition [34]). In Refs. [20,32,33], the behavioral effect of disinhibition

Box 1. Quantitative WM deficits associated with schizophrenia.

Precision. PSZ exhibits loss of WM precision [32,87–89], especially for long memory delays [88]. In computational models, this effect can be accounted for by an increased E/I ratio due to NMDAR hypofunction at interneurons [20,32,33,88], decreased E/I ratio due to NMDAR hypofunction at pyramidal neurons (Figure 2), dopaminergic imbalances [90], or the disruption of STP [33,74].

Distractibility. Memory reports of PSZ, relative to healthy controls, are substantially more biased toward distractors [32,88]. This effect has been simulated in network models with increased E/I ratio [32], decreased D1/D2 ratio [21,91,92], and disrupted STP [74]. In addition to enhanced biases toward distractors, PSZ also exhibit occasional substantial repulsion from nearby distractors [32,88]. This effect cannot be accounted for by attractor models of WM [88], but it is still unclear if it is a delay-dependent effect or it reflects alterations in perceptual processing. Indeed, experimental protocols that separate perceptual and WM origins (by including a 0-delay condition, for instance) when measuring distractibility [93] and serial dependence [33,94–96] in healthy controls have suggested a perceptual origin of similar repulsive biases.

Capacity. Reduced WM capacity characterizes PSZ [97–100]. Computational models show that WM capacity may be determined by multiple factors: interference between memories [93,101–103], memory forgetting [102–104], feature-binding errors or swap errors [105], and the spontaneous generation of false memories [22]. Some of these factors have been reported to be affected in PSZ, like increased incidence of false memories [106], but more studies are needed to better specify the origin of reduced WM capacity in PSZ. In line with all these different factors, also multiple biological mechanisms may underlie WM capacity deficits in PSZ: reduced E/I ratio [37,102,104], dopaminergic imbalances [90], reduced efficacy of top-down inputs [104], functional cortico-cortical disconnection [103], impaired oscillatory dynamics [107,108]. More sophisticated experiments and appropriate data analyses will be key in disentangling the different origins and mechanisms of reduced WM capacity in PSZ.

Serial dependence or proactive interference. Tasks engaging WM induce across-trial interference in what is commonly called *serial dependence* [109]. In contrast with the biases previously described in this box, serial dependence is *reduced* in PSZ [33] — intriguingly, this reduction also characterizes autism [110]. Attractor models with STP have been proposed for serial dependence [75,76], and it has been shown that, in these models, alterations in STP, but not in the E/I ratio of the attractor models, can account for reduced serial dependence in PSZ [33].

occurs through stronger bumps of activity (*bump attractors*), i.e. higher network activation and deeper attractors. The finding that deeper attractors are more sensitive to noisy fluctuations, causing a reduction in WM precision, is in contradiction with an intuitive understanding of dynamics in mnemonic attractor landscapes, i.e. that deeper attractors should be associated with more stable memories. This apparent paradox is resolved by noting that in continuous attractor models, random displacements of a bump attractor occur along the dimension of marginal stability (pink manifold in Figure 1B), rather than through jumps from one attractor basin to the other, as observed in discrete attractor models that are commonly used to model alternative-choice WM tasks [15]. Therefore, random bump-attractor displacements underlying WM imprecision are not exclusively linked to the depth or shape of the attractor but also depend rather intricately on the amplitude and correlations of noise in the network (see below). The fact that we do not know how NMDAR blockade affects these elements both in the brain and in biologically realistic computational models is at the heart of our current inability to unambiguously evaluate the plausibility of the glutamatergic explanation for a drop in WM precision in PSZ, as we show in the following.

Mathematical analyses of neural field models show that stronger bumps (wider and/or taller) diffuse more slowly, but this can be offset by an increase in noise amplitude or spatial correlation in the network [35,36]. The diffusivity (D) of the bump attractor is proportional

to the noise strength (ϵ) and the spatial modulation of noise correlations (ΔC) in input currents and depends inversely on the squared amplitude (A^2) of the bump [36,37]:

$$D \sim \frac{\epsilon \cdot \Delta C}{A^2} \quad (1)$$

As a result, the specific effect of reduced NMDAR efficacy, or any other manipulation of a given biophysical parameter, on WM diffusion will depend on how the manipulation affects each of these three factors quantitatively. These effects, in turn, are determined by biophysical details of the models, including the origin of correlated noisy fluctuations during the delay period. Only recently have some studies started to address the generation of correlated variability in spatially extended balanced networks [38–40], but more work is needed to fully understand how it changes with specific manipulations of biological parameters.

Specific bump attractor network implementations illustrate the indecisiveness of current modeling accounts of WM precision in PSZ. We simulated two distinct biophysical bump attractor models, which differ fundamentally in the way that noise is generated in the network (github.com/comptelab/attractorSZ for implementation details). In Model 1, noise is injected from external sources, and all-to-all coupling between neurons generates strong noise correlations [33]. We implemented two versions of Model 1: one that has

been prominently used to simulate the effects of NMDAR dysfunction on WM in PSZ [20,32] and a second version that includes an additional STP mechanism at recurrent excitatory synapses [33]. Model 2 also includes STP, but its noise is generated internally by virtue of sparse network connectivity that induces very weak correlations between the noise experienced by different neurons [41]. In Model 1, manipulations of NMDAR efficacy affected bump shape but did not change bump amplitude or mean neural variability strongly (Figure 2a and b, middle, top) but in turn had an important effect on the spatial modulation of spike-count noise correlations (Figure 2c, middle, top). In contrast, manipulations of NMDARs in Model 2 had a strong impact on bump amplitude (Figure 2a, bottom) and a more modest influence on noise amplitude (Figure 2b, bottom) and the spatial modulation of noise correlations (Figure 2c, bottom). Repeated simulations show that corresponding perturbations in NMDARs (either on excitatory cells or on inhibitory cells) in these two biophysical models led to opposing predictions for bump diffusion. Disinhibition ($E \rightarrow I \downarrow$) led to faster diffusion in Model 1 (Figure 2d, middle, top, similar to previous models in Refs. [20,32]) but resulted in slower diffusion in Model 2 (Figure 2d, bottom). Importantly, we could predict qualitative differences in diffusivity as dictated by Eq. (1) [36] (Figure 2d, dotted lines) from bump amplitude, mean neural variability, and noise correlation estimations from simulated data (Figure 2a-c). To be noted here is that these estimations were calculated from neuronal spiking activity rather than input currents as used in the mathematical derivation of Eq. (1) [36,37]. This facilitates the comparison of these results with experimental data. The results of our simulations indicate that the direction in which alterations of the E/I ratio through NMDAR hypofunction affect WM precision will depend on the biophysical details of the WM-maintaining circuit and on how these mechanisms affect bump shape, neural variability, and the spatial modulation of noise correlations. Which biological parameters determine how the bump shape and noise characteristics respond to perturbations is currently unclear, but candidate factors that distinguish the two models include sparseness of connectivity, strength of external noisy inputs, saturation of NMDARs, conductance-based synapses, and oscillatory activity.

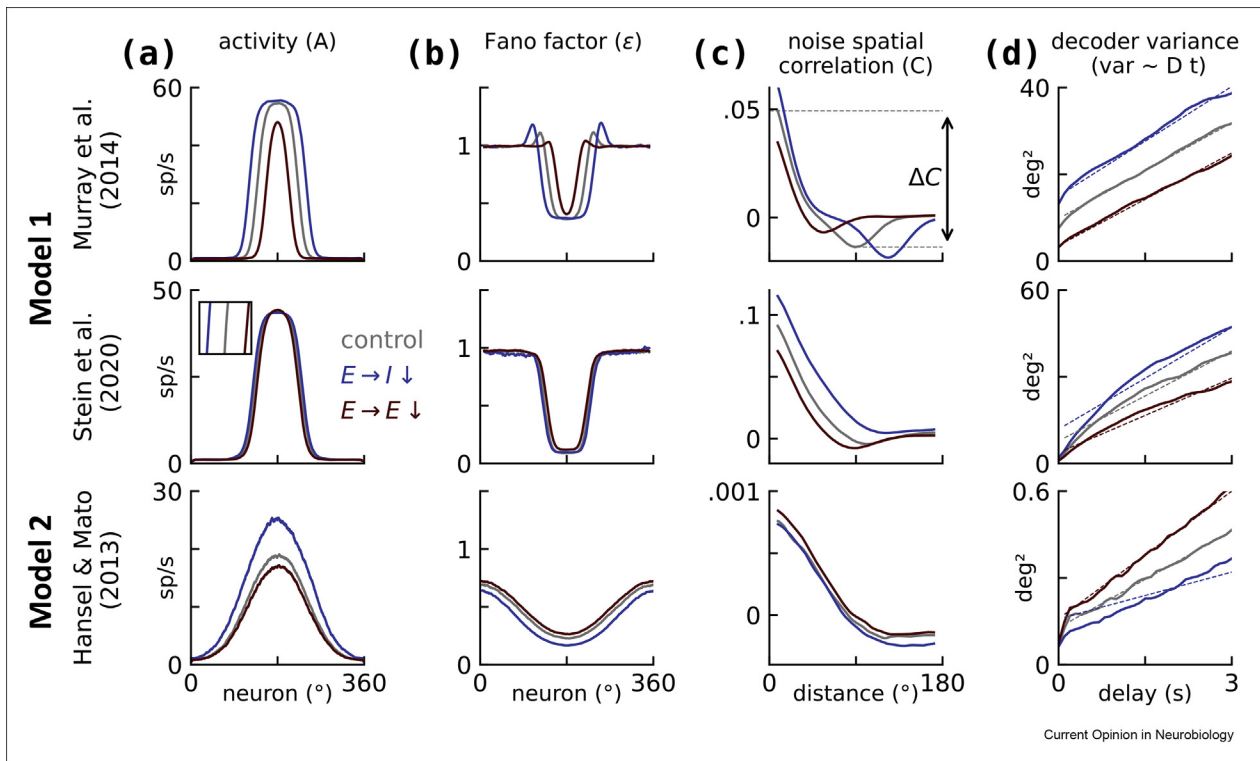
Insufficient and inconsistent experimental constraints on biologically plausible computational models

A detailed understanding of how a diversity of biologically plausible network models (including the models highlighted above) react to mechanistic manipulations can be exploited to identify the regime in which cortical circuits operate and motivate neurophysiological and pharmacological experiments in behaving animals.

Current evidence from combined pharmacology and electrophysiology underscores the insufficiency of assuming a straightforward relation between E/I ratio and WM precision: A recent study that raised the E/I ratio in monkeys through cholinergic neuromodulation by microstimulation of nucleus basalis shows that WM precision increases and tuning curves in the prefrontal cortex (PFC) become wider [42], in agreement with the impact of bump attractor shape on WM diffusivity according to Eq. (1). However, a recent study under ketamine showed a similar reduction in delay-period tuning in PFC, but this time associated with decreased precision [43], which suggests that manipulation of NMDARs may have an important impact on noise parameters [44,45] that compensate for the influence of bump shape on diffusivity (as for Model 1 in Figure 2). The opposing effects of E/I ratio on WM performance in Refs. [42,43] suggest that the convenient interpretation of functional alterations as the effect of modulations in E/I ratio via distinct convergent mechanistic manipulations may be an inadequate simplification of the mechanistic basis of cognitive deficits of PSZ. Future experiments with neuromodulators or receptor antagonists should explicitly assess the impact on bump shape and correlated noise during delay activity, together with WM precision, in order to clarify the validity of the E/I ratio as a useful construct for the interpretation of these data.

A useful approach for understanding the effects of NMDAR hypofunction in PSZ is the pharmacological administration of NMDAR antagonists [46]. Mimicking effects in PSZ, NMDAR antagonists cause reduced accuracy in WM tasks [10,25,43,47], possibly reflecting a drop in WM precision. Despite the dominant view that systemic ketamine generally raises the E/I ratio and disinhibits cortical networks [11,26,27,48,49], more specific evidence indicates that in the context of WM tasks, prefrontal delay activity is often suppressed in PSZ [50,51] and under systemic NMDAR blockade [10,43,47,52,53] (but see Ref. [44]). Yet, it has to be noted that some of the most compelling evidence for NMDAR-blockade-related suppression of delay activity in PFC comes from iontophoresis studies. Importantly, iontophoresis only affects receptors in the very near neighborhood of the electrode tip [10,54], so that its suppressive effects cannot be unequivocally associated with the network effects of systemic administration, as illustrated in simulations in Figure 3. Indeed, when NMDAR antagonism is more effective on interneuron receptors than on pyramidal neuron receptors, iontophoresis vs. systemic administration simulations yield paradoxical results: iontophoresis suppresses (Figure 3c and d), whereas whole-network application enhances delay activity (Figure 3b). Electrophysiology studies in monkeys performing a WM task under systemic NMDAR antagonists have mostly found decreased [10,43,52] but

Figure 2



Different biophysical network models yield opposing predictions on how the E/I ratio affects WM precision. We tested two different biophysical models of spatial WM. *Model 1* (upper two rows [20,33]) has been predominantly used to investigate effects of NMDAR hypofunction on WM and is characterized by all-to-all connectivity, conductance-based synapses, saturating NMDARs, noisy inputs [33], and may include STP in excitatory synapses (middle row, ref. [33]) or not (top row, ref. [20]). *Model 2* (lower panel row, ref. [41]) is an alternative model: sparse connectivity, current-based synapses, nonsaturating NMDARs, internal generation of noise [41]. E/I ratio was modulated by reducing the efficacy of NMDARs on excitatory neurons ($E \rightarrow E \downarrow$, resulting in reduced E/I ratio ($E/I \downarrow$)) or on inhibitory neurons ($E \rightarrow I \downarrow$, causing $E/I \uparrow$). The two network models responded very differently to these manipulations: with little effect on bump amplitude and strong impact on noise parameters (model 1) or with strong impact on bump shape but minor effects on noise parameters (model 2). As a result, the diffusivity of memory encoding increased with the E/I ratio for model 1 but decreased with the E/I ratio for model 2, in agreement with mathematical derivations of how diffusivity depends on bump strength (A), noise amplitude (ϵ), and the modulation of the spatial correlation of noisy fluctuations (ΔC) (Eq. (1) [36]). We estimated the parameters A , ϵ and ΔC from neuron spike counts (the mathematical formula is derived for input currents) through the range of spike counts in the bump, the Fano factor of spike count across trials, and the spatial pattern of spike-count noise correlations in the bump, respectively. These estimates led to predicted red and blue slopes (dotted straight lines), where intercepts and gray slopes were independently fitted to simulation data. **(a)** population activity during the delay for simulations with cue stimulus at 180° (A : amplitude of tuning in activity); **(b)** Fano factor (variance over mean across trials) of spike counts of excitatory neurons (100 ms window, 1 s into the delay) (ϵ : mean Fano factor across neurons); **(c)** spatial correlation of fluctuations around the mean for spike-counts in the delay (100 ms window, 1 s into the delay) (ΔC : amplitude of tuning in noise correlations). Note the large quantitative difference between the two models due to dense versus sparse connectivity [40]. Of significance for bump diffusivity is the modulation of the spatial correlation ΔC ; **(d)** memory diffusion computed as the time-by-time variance of population vector decoding of bump centers (250 ms windows) for 1250 different simulations in 3 s long delay periods. For model 2, systematic drifts [41] were removed by subtracting the mean decoder trajectory of 25 simulations with identical cue stimulus, and for 50 different cue stimuli, before computing the variance. For visualization purposes, high heterogeneity in neuron rates in model 2 was smoothed with a Gaussian kernel in **a-c**. Details of network simulations and analyses are available at <https://github.com/comptelab/attractorSZ>.

also increased [44] prefrontal mnemonic activity. Such experiments are critical in clarifying the impact of systemic NMDAR antagonists on WM representations and properly constrain computational models (Figure 2).

Another factor that complicates the understanding of the effects of NMDAR hypofunction in PSZ on WM is the distributed nature of WM activity across the cortex. Based on currently available evidence, NMDAR antagonists would suppress prefrontal WM-related activity [10,43,47,52,53]. Recent evidence, however, also shows

that WM deficits of PSZ may depend particularly on activity in parietal circuits [55]. Interestingly, NMDAR antagonists affect mnemonic activity in prefrontal and parietal circuits inversely [52], suggesting a possible enhancement of parietal WM-related activity. This contrast in the reaction of these two circuits to NMDAR manipulation is supported by marked differences in cellular physiological properties [56], which could impose different correlated noise structures (Figure 2). Which of the two areas is more directly linked to WM behavioral output? There is evidence that prefrontal

mnemonic activity reflects the memory diffusion that causes WM imprecisions [57,58], suggesting a closer link of this area to WM precision. However, it is not known if this relationship also exists for activity fluctuations in the parietal cortex and which of the two areas is more closely associated with the activity drifts that drive WM imprecisions. As a result, specifying the dominant role of prefrontal or parietal circuits in maintaining accurate spatial WM signals through the mnemonic delay appears here as another key piece of information to constrain currently indecisive computational models (Figure 2).

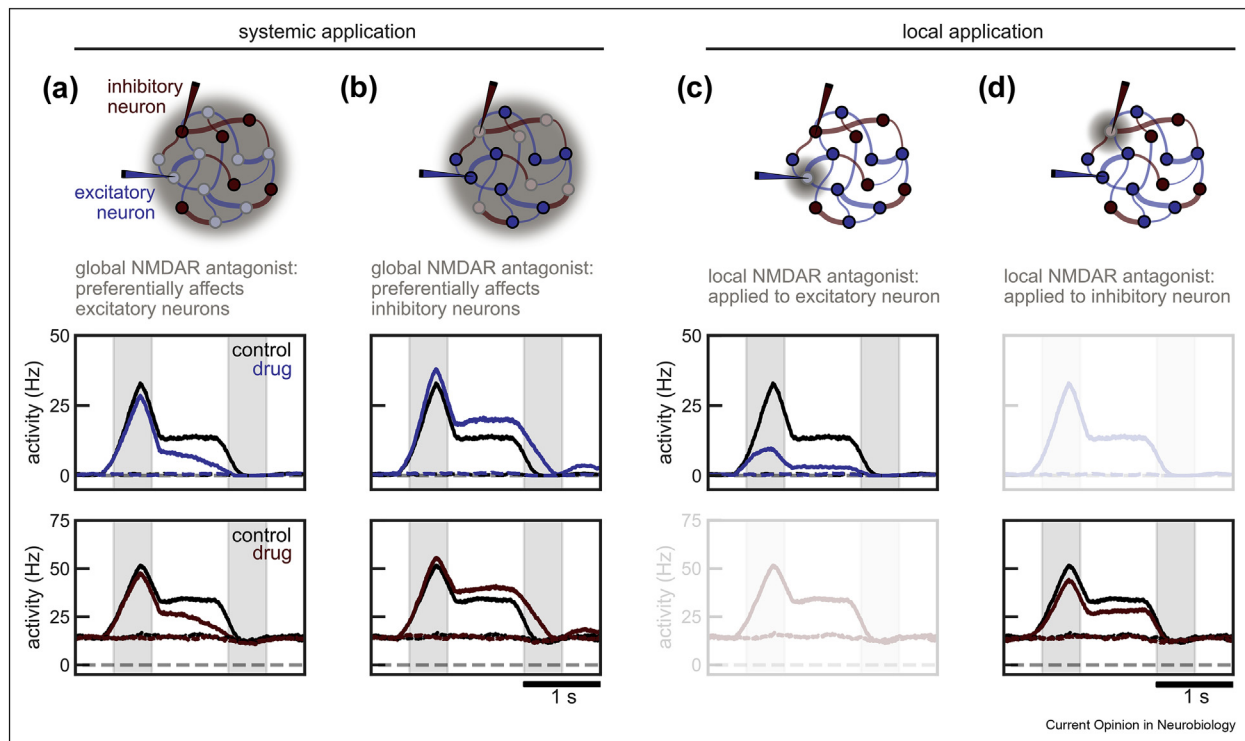
Beyond E/I ratio: plasticity deficits in schizophrenia and their effects on WM

On the basis of insufficiently constrained computational models, it is currently unclear how regional imbalances in cortical E/I ratio caused by hypofunctional NMDARs can explain WM precision deficits in PSZ. However, mechanisms beyond a shift in cortical E/I ratio could be affected by biological alterations in PSZ, some of which might be mapped on WM deficits more unequivocally than the concept of cortical E/I ratio. Here, we consider a synaptic plasticity mechanism that explains reductions in

WM precision in both attractor models considered in Figure 2. Schizophrenia has been related to dysfunctions in synaptic plasticity [59–62], and perceptual and neurocognitive alterations in the disease have been attributed to alterations in long- and short-term plasticity (STP) [63–65], also in relation to NMDAR hypofunction [66,67]. Cognitive effects of disrupted STP on WM have been assessed in genetic mouse models [68,69] and computational models of schizophrenia [70], where reductions in STP lead to reduced WM performance [68,69]. Moreover, pharmacological inhibition of NMDARs through systemic ketamine administration decreases spike-time synchrony in delay-active cells in PFC during WM [71], which could be interpreted in light of reduced prefrontal STP [72]. Finally, computational modeling links a novel behavioral pattern of reduced serial dependence in PSZ and anti-NMDAR encephalitis to dysfunctional STP, while prefrontal E/I ratio alone cannot account for these behavioral findings [33].

The predictions for the effect of STP on WM are clear: when implemented in bump attractor networks, STP stabilizes bump attractors against noise so that memory

Figure 3



Dissociated effects of systemic vs. local application of NMDAR antagonists in a computational WM model. Depending on whether NMDAR blockade affects receptors more strongly in excitatory neurons than in inhibitory neurons, or vice versa, delay-period activity in network simulations gets reduced (a) or enhanced (b) for both excitatory (top graphs, blue) or inhibitory (bottom graphs, red) neurons. In contrast, the local application of NMDAR antagonists invariably reduces delay-period activity in the affected neurons (c) top, (d) bottom while global network dynamics remain unaltered, as reflected in the activity of nonmodified neurons, which are usually not recorded during iontophoresis ((c) bottom, (d) top). Solid lines, the activity of one neuron after the presentation of a preferred stimulus; dashed lines, the activity of one neuron after a nonpreferred stimulus. Details of network simulations are available at <https://github.com/comptelab/attractorSZ>.

precision is better maintained through delay periods [41,73,74], and bumps are more robust against intervening distractors [74]. Further, STP induces serial dependence between successive WM trials because of the enduring synaptic trace that influences subsequent bump attractor memories [33,72,75,76]. STP has these effects irrespectively of the specific network implementation of the bump attractor, and as a result, its deficit leads unambiguously to WM precision loss (Figure 4), increased distractibility [74], and reduced serial dependence [33], all characteristic WM alterations in PSZ (Box 1). Interestingly, this mechanism contributes weakly to delay-period activity, so its disruption could occur independently and in addition to biological alterations that impact the E/I ratio (Figure 4). For instance, assuming network disinhibition in the circuit responsible for maintaining WM (possibly parietal cortex), Model 2 in Figure 2 would not be able to explain a reduction in WM precision through the alteration in E/I ratio, but it could if in addition, it had reduced STP (Figure 4). Conversely, network inhibition as currently considered for prefrontal WM circuits in PSZ would make Model 1 in Figure 2 unable to account for WM precision loss unless STP reductions are additionally considered (not shown). In fact, it is not unlikely that changes in neuromodulatory or neurotransmitter systems would affect both E/I ratio and synaptic plasticity, with a potential interdependence of the two phenomena [77]. These scenarios may reconcile possible inconsistencies between experimental evidence and computational

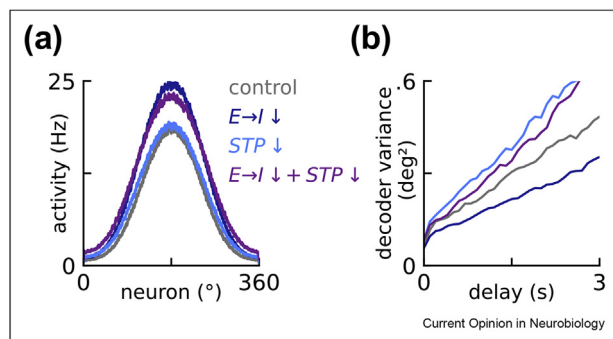
models of schizophrenia when interpretations only consider imbalances in the E/I ratio (Figure 2).

Conclusions

In this review, we argue that although contemporary network models of schizophrenia capture WM deficits observed in PSZ, the space of possible modeling solutions is not sufficiently constrained by experimental data. By focusing on the effect of increased vs. decreased E/I ratio ($E \rightarrow I \downarrow$ vs. $E \rightarrow E \downarrow$) on WM precision, we provide two general insights. First, these opposed manipulations can produce the same behavioral pattern in different alternative, plausible biological network models (Figure 2). As a result, the interpretations of mechanistic models in computational psychiatry will remain limited in the absence of properly constraining experimental data. Importantly, in-depth analysis of computational models can guide the design of critically informative experiments. Second, we argue that grouping different perturbations under the convenient umbrella of the E/I ratio can be inadequate in some conditions, as different pharmacological perturbations can affect the E/I ratio similarly but have opposite effects on behavior [42,43].

In the specific case of how manipulations of the E/I ratio affect WM precision, we point out four important neurophysiological unknowns: The shape of activity bumps during WM delays, the specific properties of correlated noise in the circuit, the specific brain area responsible for maintaining accurate WM representations, and the possible joint alteration of NMDARs and STP. First, it appears critical to determine the fine-grained effects of pharmacological interventions on neural tuning. Measuring tuning properties together with behavioral effects will be necessary to inform model selection. Second, spatial profiles of noise correlations may be critical for understanding the effect of disease mechanisms on WM precision, and potentially other WM phenomena not tested in this paper. Third, these neurophysiological characterizations should be done in the circuits most directly associated with maintaining precise WM, as current evidence comparing prefrontal and parietal cortices shows that they respond very differently to NMDAR antagonists. Pharmacological experiments *in vivo* will be key to inform computational models of schizophrenia by systematically measuring these fine-grained neurophysiological effects directly in the area responsible for WM maintenance. Finally, *in vitro* experiments should determine if NMDAR antagonists also impact slower mechanisms (e.g. different types of STP [78]) in WM-related cortical networks, as computational models unequivocally assign a memory-stabilizing role to such slower mechanisms, and this could interact with interpretations of WM precision deficits in PSZ (Figure 4).

Figure 4



In network models, reductions of STP cause WM precision loss, also with concurrent E/I ratio alterations that would increase WM precision on their own. Simulations correspond to network Model 2 of Figure 2. Control and $E \rightarrow I \downarrow$ conditions are shared with Figure 2, and are compared here with simulations with additional reduction in STP ($STP \downarrow$ and $E \rightarrow I \downarrow + STP \downarrow$, respectively). (a) Average delay-period activity of neurons in the network in each condition. Notice that STP reduction causes minimal changes in delay rates in the simulations, indicating quite intact E/I ratio in the delay period after STP reduction. (b) Memory diffusion patterns for each condition (see Figure 2d). Notice the strong impact of STP reduction on memory diffusion, to the point that it turns reduced diffusion of $E \rightarrow I \downarrow$ into enhanced diffusion ($E \rightarrow I \downarrow + STP \downarrow$) compared to control diffusion (gray).

There is also pending work on the computational and theoretical front. Shared correlations, in addition to the commonly considered bump attractor shape [20], impact WM precision [36], and only recently have studies started to address how these shared correlations are generated in recurrently coupled networks [39,40]. Theoretical efforts should continue and also extend to bump attractors, eventually aiming to understand the role of biophysical mechanisms that have been implicated in schizophrenia, such as NMDARs, dopamine, or STP. Importantly, insights gained about how biophysical manipulations impact bump tuning and noise properties in WM are expected to generalize to other behavioral contexts governed by continuous attractor dynamics, such as tactile WM [79] or the thalamic head direction system in the absence of input [14]. Furthermore, PSZ show abnormal behavioral patterns in other cognitive tasks that require context-dependent cognitive control and have been linked to altered E/I ratio [80–82]. Developing biophysical computational models would allow the mechanistic understanding of these deficits through the consistent integration of computational and neurophysiology data, as attempted here for spatial WM precision. Recurrent neural networks (RNNs) trained with backpropagation are a possible tool to address more complex tasks that are difficult to model in a bottom-up fashion [83]. Training RNNs to replicate behavioral patterns and neural dynamics in PSZ, or pharmacological models of schizophrenia, could untie different contributions of structured connectivity (Ehrlich et al. abstract 1-052, Computational and Systems Neuroscience (Cosyne) Conference, February 2021) [84,85] and STP [86], which appear as the key ingredients to understand WM deficits, and perhaps cognition more broadly, in PSZ.

Finally, we want to acknowledge the contribution of computational models of disease to the understanding of neuropsychiatric disorders. While pointing out inadequacies of current models to provide a consistent account of cognitive deficits in PSZ, we also showed how the analysis of these models allows a more precise framing of the research questions to advance concertedly toward a mechanistic understanding of these diseases. This underscores the rigor that mathematical modeling adds to the field of psychiatry, and we hope that it encourages clinical researchers to adopt these models as a formal framework to understand the disease.

Conflict of interest statement

Nothing declared.

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- * of special interest
- ** of outstanding interest

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