



RESEARCH ARTICLE

REVISED Neuromodulation influences synchronization and intrinsic read-out [version 2; peer review: 2 approved, 1 approved with reservations, 1 not approved]

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Abstract

Background: The roles of neuromodulation in a neural network, such as in a cortical microcolumn, are still incompletely understood. Neuromodulation influences neural processing by presynaptic and postsynaptic regulation of synaptic efficacy. Neuromodulation also affects ion channels and intrinsic excitability.

Methods: Synaptic efficacy modulation is an effective way to rapidly alter network density and topology. We alter network topology and density to measure the effect on spike synchronization. We also operate with differently parameterized neuron models which alter the neuron's intrinsic excitability, i.e., activation function.

Results: We find that (a) fast synaptic efficacy modulation influences the amount of correlated spiking in a network. Also, (b) synchronization in a network influences the read-out of intrinsic properties. Highly synchronous input drives neurons, such that differences in intrinsic properties disappear, while asynchronous input lets intrinsic properties determine output behavior. Thus, altering network topology can alter the balance between intrinsically vs. synaptically driven network activity.

Conclusion: We conclude that neuromodulation may allow a network to shift between a more synchronized transmission mode and a more asynchronous intrinsic read-out mode. This has significant implications for our understanding of the flexibility of cortical computations.

Keywords

neuromodulation, synchronization, network topology, synaptic efficacy, intrinsic excitability, asynchronous, activation function

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REVISED Amendments from Version 1

- I left the title unchanged, since it captures both the effect of neuromodulation on correlations and the way information is read out and routed under different synchronization regimes.
- The abstract was changed and partly rewritten to make the difference between methods and results clearer.
- The I_A ion channel was an example for realistic modification of a neuron by 50% variation in ion channel expression, which we derived from an earlier paper (Scheler, 2014). Neuromodulation often affects just one type of ion channel, and a total variation of 30–50% seems realistic. Instead of continuing with variations over all ion channels in a conductance-based neuron model, we then showed that we can achieve the same effect with a simplified neuron model (Izhikevich, 2004) by modifying its abstract parameters. This has been clarified in the text now.
- I have slightly extended some table and figure captions.
- Figures have been colored to improve expressiveness.
- Many small changes, clarifications, additional references etc. were included as suggested by the reviewers.

See referee reports

Introduction

In this paper we present a realistic network model, akin to a cortical microcolumn¹⁻⁴, and investigate its properties under the assumption of fast synaptic and intrinsic modulation as evidenced by neuromodulation⁵. We hypothesize that rapid synaptic efficacy changes allow a network to operate with different topologies, and that network topology is a decisive factor towards creating and sustaining synchronized inputs vs. producing asynchronous input.

We have previously shown for a conductance-based neural model of striatal medium spiny neurons that neuronal heterogeneity expressed by the contribution of individual ion channels (such as delayed rectifier potassium channels or GIRK channels) may still result in uniform responses, if the neurons are driven with highly correlated synaptic input. If the same neurons are driven by more asynchronous, distributed synaptic input, the heterogeneity is manifest in the response patterns, i.e. the spike rates and the timing of the spikes (see 6). These results were achieved using conductance-based point neurons⁶. Here we use two-dimensional neural models⁷ to further investigate the effect and determine its significance in the context of a cortical neural network.

Due to Hebbian learning^{8,9}, under normal conditions synaptic weights follow a lognormal distribution, which results in graphs with a heavy tail degree distribution. Degree modification by rapid synaptic efficacy changes would not only allow for alterations to the density, but also the topology of the connecting graph. In this paper we examine the hypothesis that such changes in network topology actually occur, driven by neuromodulatory effects on presynaptic release or postsynaptic response^{5,10-12}. We analyze this situation with two example graphs, and we also perform further analysis to show that there is a continuum of graphs which can be reached by rapid synaptic changes.

Methods

Conductance-based neuron model and synaptic input

The conductance-based neural model of a striatal medium spiny neuron is described in detail in 6. The membrane voltage V_m is modeled using the equation

$$\dot{V}_m = -\frac{1}{C} [\mu_1(I_1) + \mu_2(I_2) + \dots + \mu_n(I_n) - I_{syn}], \quad (1)$$

where the I_i are the currents, induced by the individual ion channels. Variability of the neuron is modeled by modifications to μ_i . This model includes ion channels for Na (INa), K (IK), slow A-type K channels (IAs), fast A-type K channels (IAf), inward rectifying K channels (IKir), L-type calcium channels (ICaL), and the leak current (I_{leak}). The definition of all parameters and the dynamics of the ion channels can be found in 6.

For the experiments in this paper, we use only a single channel as an example for the variability that can be induced by neuromodulatory changes. We chose the slow A-type K channels as in 6. The total current contribution for this channel is μ_{IAs} where μ was selected between 1.0 and 1.5, a variability by $\pm 25\%$.

In order to illustrate the variability in neuron behavior, we excited the neuron model by input signals, resembling two kinds of synaptic input: uncorrelated and correlated. These signals were generated by superposition of excitatory and inhibitory spikes from individual Poisson-distributed spike trains (50 excitatory and 10 inhibitory), and biased Gaussian background noise. The details can be found in 6. The amount of pairwise correlation in these spike trains governs the type of input signal. A high correlation factor was used in order to generate sequences which have short periods (10–15ms) of high activity.

Heterogeneity in a two-dimensional model

In order to do large-scale simulations we needed to employ a simple, computationally tractable neuron model. We used a two-dimensional model of a neural oscillator (cf. 7), and employed an instantiation of the model with parameters fitted to the general properties of cortical pyramidal neurons¹³ as a generic model (g). The model consists of an equation for the membrane model v (Equation 2), fitted to experimental values for cortical pyramidal neurons, and an equation for a gating variable u (Equation 3).

$$\dot{v} = 0.04v^2 + 5v + 140 - u - I_{syn} \quad (2)$$

$$\dot{u} = a(bv - u) \quad (3)$$

$$b = 0.2$$

$$a = 0.02$$

When the neuron fires a spike (defined as $v(t) = 30mV$), v is set back to a low membrane potential $v := c$; $c = -65.8mV$ and the gating variable u is increased by a fixed amount d ($u := u + d$; $d = 8$) (cf. 13). This formulation allows for a very simple neuron model, which avoids the explicit modeling of the downslope of the action potential, and rather resets the voltage. Time-dependence after a spike is modeled by the gating variable u .

Neuronal heterogeneity is achieved by systematic variation of inactivation parameters. By varying d , we can vary the inactivation dynamics of the model after a spike, by varying a we vary the activation/inactivation dynamics for u . In this way, we can model neuronal variability of activation/inactivation dynamics, which is sufficient to model frequency-selectivity as a stored intrinsic property. The parameters used in this paper for different neuron types are listed in [Table 1](#).

Graph properties

We created graphs of N ($= 210$) excitatory neurons, and K (≈ 1900) excitatory connections. For the excitatory neurons, we use randomly connected graphs (N,K) with different width $\sigma^* = e^\sigma$ (σ = standard deviation) of the degree distribution. This corresponds to normal (Gaussian) to lognormal graphs with different widths and length of the heavy tail. We model inhibition by Poisson-distributed inhibitory synaptic input directly onto excitatory neurons.

We use specific instantiations of these graphs (RG, LG1) for the simulations. [Table 2](#) shows global graph characteristics for the Gaussian graph (RG), the lognormal graphs (LG1), and intermediate graphs LG2, LG3, and LG4.

The rewiring algorithm used to change the properties of a graph G is a greedy algorithm, which iteratively selects the node with the highest degree. One of its edges is then rewired to random nodes with lower degrees, decreasing σ^* . The algorithm terminates, when the value of σ^* falls below a given threshold.

Definitions

We define synchronization s in a network by pairwise correlations: for each neuron n_i , we count, for each other neuron n_j , the number of spikes which occur within a window W ($W = 10ms$) of n_i 's spike events, divided by the total number of spikes for n_i . More precisely, for each neuron, we bin all firing events into 5ms bins. We then count the number of spikes emitted by other neurons, which fire in a 10ms window around the (start) of the bin. The synchronization s is then the average over all neuron pairs in the network:

$$s = \frac{1}{N(N-1)} \sum_j \frac{1}{S_j} \sum_i B_{ij},$$

where B_{ij} is the number of spikes that neurons i and j have in common within a moving window of $W = 10ms$ during the entire measuring time. S_j is the number of spikes of neuron j during the entire measuring time.

Simulation tools

All simulations were performed with the software tool **CNeuroSim**, which is implemented in **Matlab** (R2016b) and C, and available at <https://doi.org/10.5281/zenodo.1164096>.

Results

Conditional expression of intrinsic excitability in conductance-based models

We show how we can model gain as a stored intrinsic property, defined as the average spike rate in response to constant input

Table 1. Parameters for different neuron types(cf. 13).

name	a	b	c	d
generic	0.02	0.2	-65	8
type1	0.025	0.2	-65	6
type2	0.02	0.2	-65	9
type3	0.015	0.2	-65	12
type4	0.015	0.15	-65	14
type5	0.022	0.3	-65	14
type6	0.022	0.3	-65	9.5

Table 2. Graph Properties for Model Networks (Excitatory Connections).

Property	RG	LG1	LG2	LG3	LG4
N no of nodes	210	210	210	210	210
K connections	1880	1924	1895	1920	2050
d density	0.042	0.043	0.043	0.043	0.047
indegree	8.95[2...17]	9.5[0...26]	9[0...24]	9.14[0...30]	9.75 [0...25]
outdegree	8.95[4...18]	9.5[0...56]	9[0...58]	9.14[0...53]	9.75 [0...54]
cluster index	0.04	0.068	0.064	0.062	0.08
mean path length	2.66	2.41	3.7	3.72	2.32
width σ^*	1.44	2.89	2.5	2.71	2.71
synchronization s	0.11	0.32	0.26	0.31	0.34

(constant input in A / average spike rate in Hz). We used a full ion channel based model (the MSN model⁶), with variation in the slow A-type potassium channel (IAs). This ion channel was used as an example for the conductance-based model⁶. Neuromodulation often affects just one type of ion channel, and a total variations of 30–50% in ion channel efficacy have been typically found.

In **Figure 1A**, we show the response of individual, unconnected MSN model neurons with a scaling of $\mu_{IAs} = 1.0, 1.3, 1.5$ to a noisy input signal, derived from simulations of neural activity as uncorrelated Poisson-distributed spiking. The top panel shows the development of the membrane potential, V_m , over time for all neurons. The middle panel shows the spike-train for each neuron with the mean interspike interval (ISI). The bottom panel shows the simulated synaptic input. The dots correspond to the spiking events for a single neuron 3 ($\mu_{IAs} = 1.5$). The resulting mean ISIs are 25, 37, and 45 ms. With a standard deviation of 6, 11, and 8, they are clearly distinguishable. This is also

shown by the Gaussian distribution for the mean ISIs for each neuron type (**Figure 1B**).

This model shows frequency-specificity as read-out of the relative contribution of the slow A-type potassium channel, indicated by the scaling factor μ_{IAs} . The relative contribution of an ion channel corresponds to its density or distribution on the somato-dendritic membrane, or in some cases its specific localization at dendritic branch points. Experimental evidence has shown that this is a plastic feature for neurons.

We then employ highly correlated synaptic input, defined as in **6** (see *Methods*). We stimulate the same neurons with the correlated input and observe the spike pattern (**Figure 2**). We can show that the frequency-specificity of the neuron disappears. Instead we see a time-locked spike pattern which is expressed by a similar spike frequency (**Figure 2A**) and an overlap of the mean ISIs (**Figure 2B**). What this experiment showed is that a

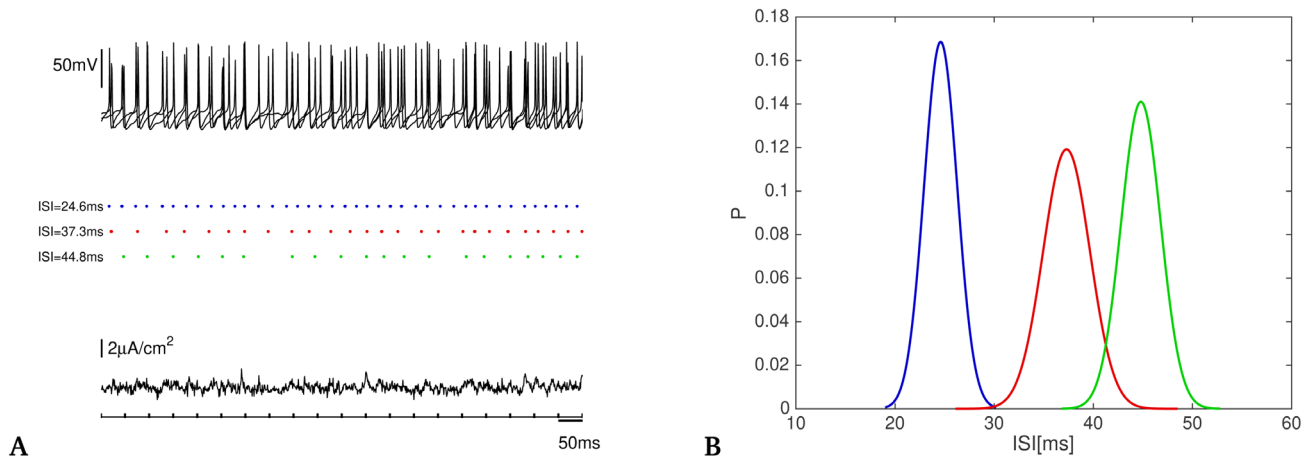


Figure 1. A. Frequency response of 3 conductance-based MSN model neurons with variable scaling of IAs to uncorrelated input **B.** Probability distributions of ISIs. We see a clear separation of frequency responses.

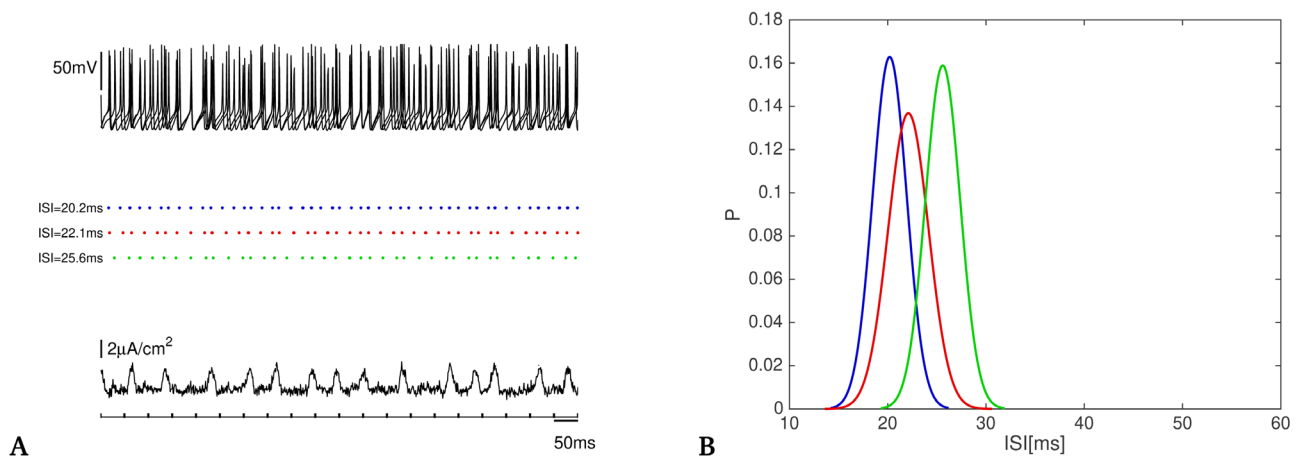


Figure 2. A. Frequency response of the same MSN model neurons as in **Figure 1** to correlated input. **B.** Probability distribution of ISIs. We see overlapping of frequency responses.

stored intrinsic property, the gain, is available to the processing network in a conditional manner. The property is continually expressed, the differences in ion channel density persist. Depending on the mode of stimulation, however, this property is manifested as intrinsic gain, or it is obscured when a neuron is driven by strongly correlated input.

Results for simplified model neurons

To continue with exploring this property of model neurons, we switched to a simplified model neuron⁷ and created a set of variations for this model (see *Methods*). We show the response of two-dimensional model neurons to asynchronous input in **Figure 3**, and to regular, synchronous input in **Figure 4**. In the first case, we have clearly separated frequencies, and in the second case, the ISIs are nearly identical with a narrow distribution. When we stimulate the neurons with irregular, but synchronous

input, the ISIs become identical, but with a wider distribution to reflect the different duration of pauses between the synchronous stimulation (**Figure 5**).

Multiplexing synchronous and asynchronous input

We may also consider the question of whether a neuron can simultaneously respond to an input and read out its stored spike frequency. If there are single synchronous events, which interrupt ongoing spiking, can we recover the intrinsic properties for each neuron? In **Figure 6** it is shown that this is possible. **Figure 6A** shows the input and the synchronous responses, and in **Figure 6B** we still see a clear separation of frequencies.

We conclude that we can multiplex asynchronous and synchronous input. It is also apparent that there needs to be a lower

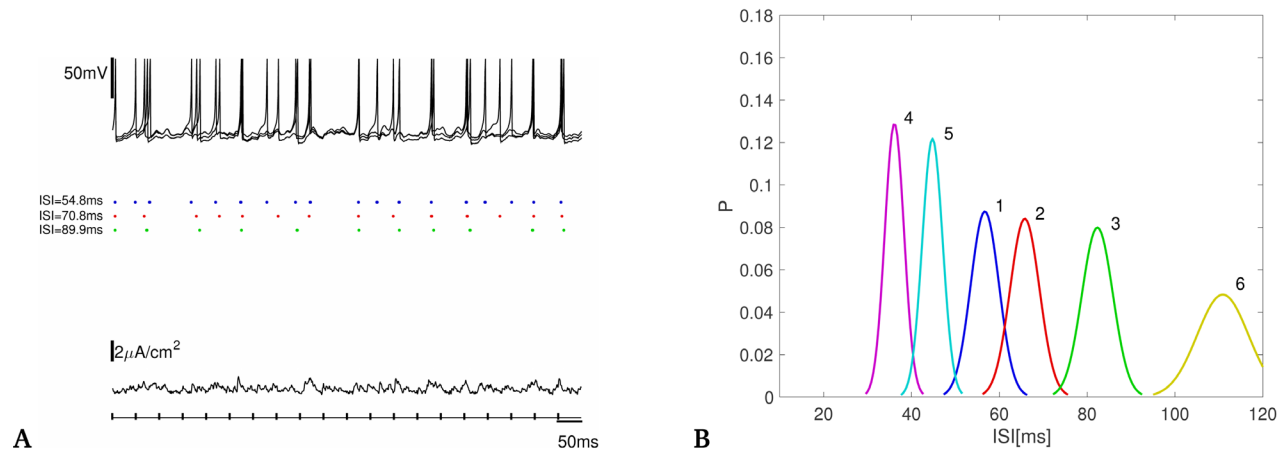


Figure 3. **A.** Spike response of the two-dimensional dynamic model neurons (1,2,3) to asynchronous input. **B.** Gaussian distributions of ISIs for six model neurons (1,2,3,4,5,6) to asynchronous input as in **A**. We see a clear separation of frequency responses for model neurons.

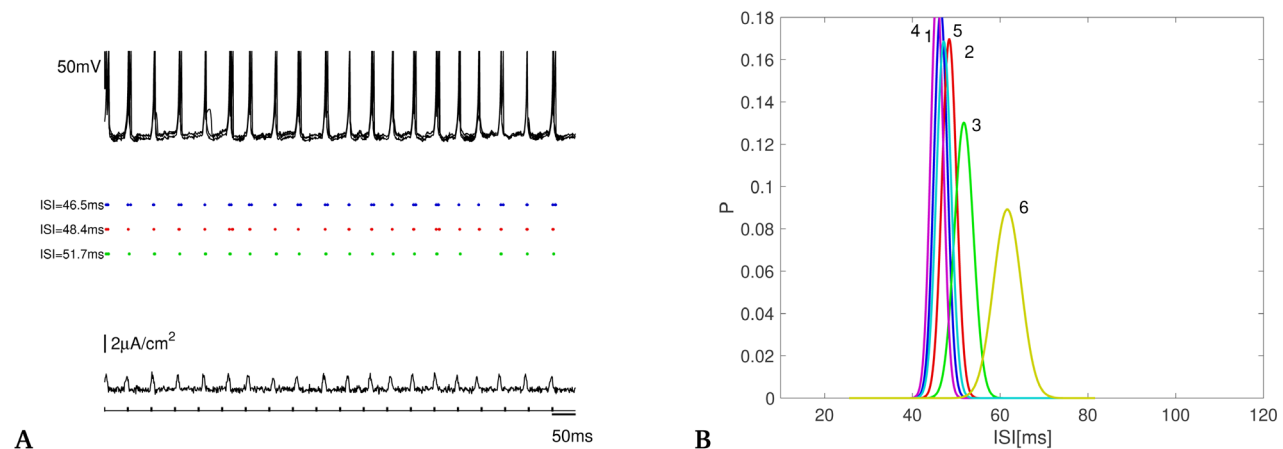


Figure 4. **A.** Spike response of the two-dimensional dynamic model neurons (1,2,3) to regularly timed, correlated input. **B.** Distributions of ISIs for six model neurons (1,2,3,4,5,6) to the same input as in **A**. We see strong overlapping of frequency responses, at about 50ms ISI, in accordance with the input. We notice that neuron 6 fires at lower frequencies than the input, it probably has a longer reset period, as seen in **Figure 3B**.

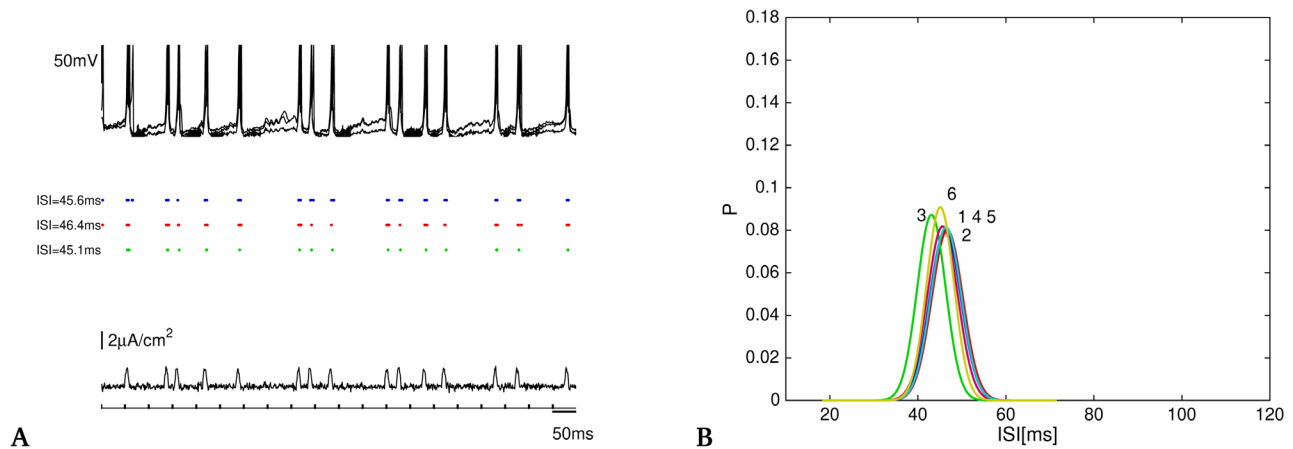


Figure 5. **A.** Spike response of the two-dimensional dynamic model neurons (1,2,3) to irregularly timed, correlated input. **B.** Gaussian distributions of ISIs for six model neurons (1,2,3,4,5,6). We see strong overlap of frequency responses.

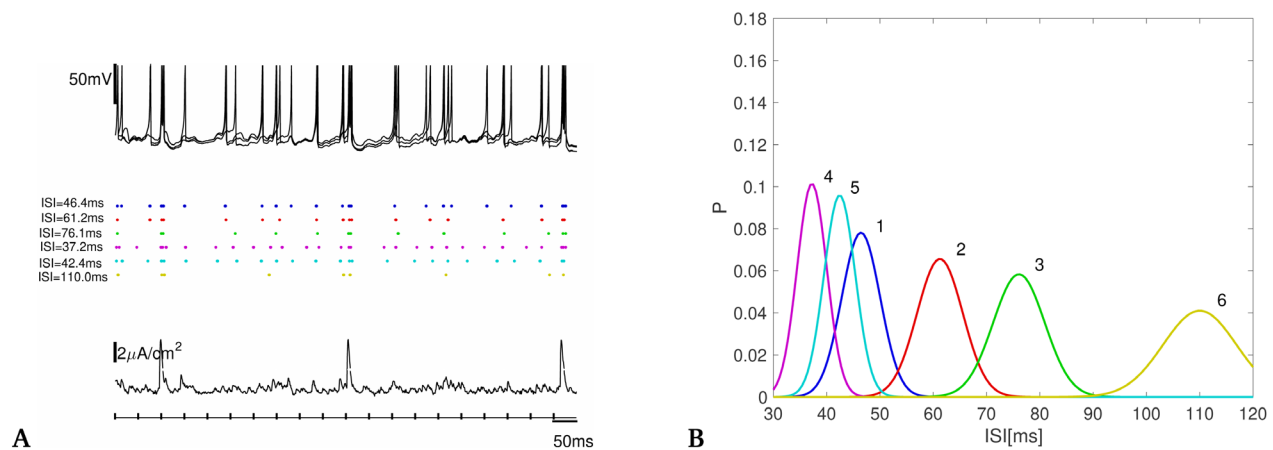


Figure 6. **A.** Multiplexed input and response of different model neurons (1-6). Three synchronous events are clearly represented in the spike pattern of all neurons. **B.** Mean ISIs for each neuron type. The separation of frequencies is kept. Compared to Figure 3B the standard deviation is somewhat higher because of the additional spikes caused by strong synchronous input.

limit on the intervals between synchronous events that can be processed without disrupting intrinsic properties. This interval needs to be defined as functionally dependent on the intrinsic frequencies. In this case, it is $3/s$ for the synchronous events, with 10Hz for the slowest neuron.

Synchronization depends on network topology

The simplified model neurons allow the creation of large networks of heterogeneous neurons and exploration of different topologies (cf. also 14,15). We hypothesized that a lognormal graph, because of its hierarchical topology and the existence of hub neurons would lead to synchronization of action potentials – even with heterogeneous neurons – while a Gaussian topology would

support asynchronous spiking behavior^{16,17}. We define synchronization s in a network by pairwise correlation (*Methods*). The spike frequency for each neuron type is assessed by the mean and standard deviation for ISIs, as before.

We first use a randomly (Gaussian) connected graph (RG) with 210 neurons ($N = 210$) and 1800 excitatory connections ($K = 1800$). We employ 7 different neuronal types (1-6, plus the generic neuron g) with 30 Neurons each (*Methods*). Figure 7A shows an excerpt of the graph structure. We can see that the graph is connected such that all neurons have a comparable number of connections. This is also apparent in Figure 8, where we can see a (narrow) normal distribution for connectivity for

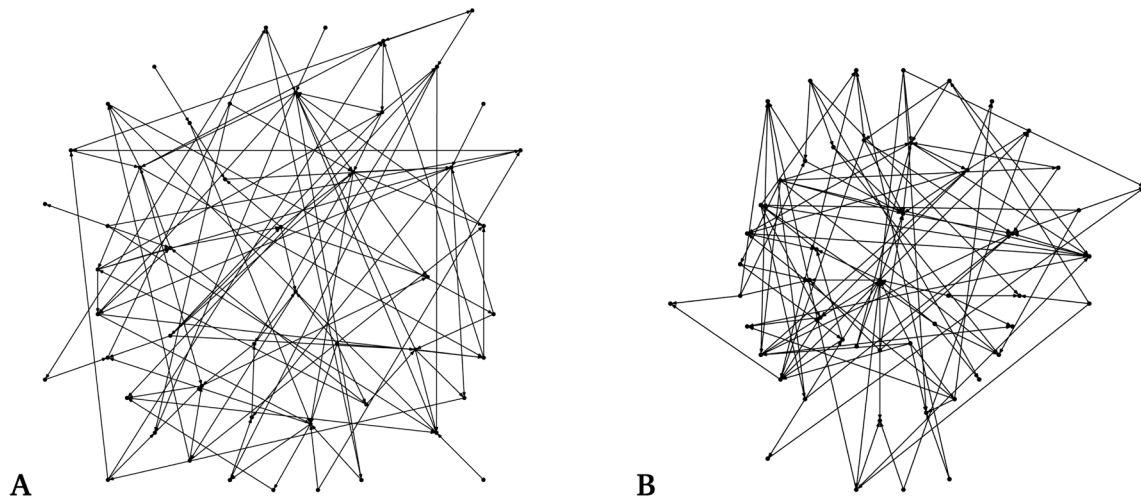


Figure 7. **A.** Part of a Gaussian Graph (RG), here for 50 neurons **B.** Part of a Lognormal Graph (LG1), for 50 neurons. The more regular, lattice-like structure of the Gaussian graph and the higher clustering and the appearance of highly connected 'hub' neurons in the lognormal graph is apparent.

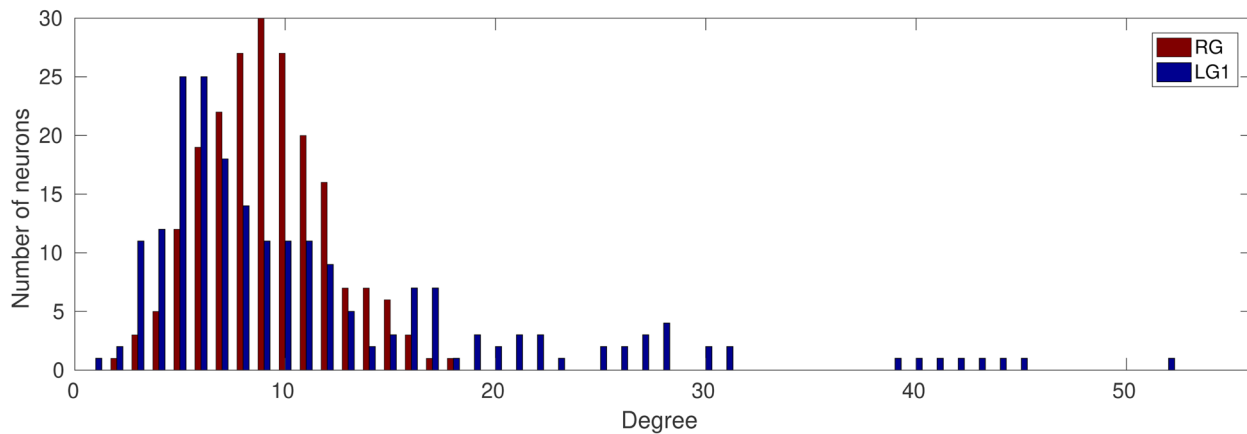


Figure 8. Degree histogram for the Gaussian Graph RG (red) and the lognormal Graph LG1 (blue). The LG has more neurons with few connections. It also has a heavy tail of neurons with 20 and more connections ('hubs'), which are lacking in the Gaussian graph.

the Gaussian graph RG. Table 2 contains the usual graph characteristics.

$N = 210$ is about the size of a minicolumn or ensemble unit within a larger network with presumably dense interconnections¹⁸. The maximal density $d = K/(N \times (N - 1))$ in a cortical microcircuit is estimated at 0.1 for 10^4 neurons, and 10^7 synaptic connections¹⁹. With $\approx 50\%$ of synapses internal to the network, $d = 0.04 - 0.07$ is a realistic value for internal connectivity¹⁸. There is also a small background inhibition to all neurons present, implemented by 10% inhibitory neurons with Poisson-distributed firing and complete connectivity to excitatory neurons.

We now stimulate the graph by an initial stimulation to 10 randomly selected excitatory neurons (for about 1 second). In Figure 9A, we see highly asynchronous neuronal activity after 1s

of stimulation. The pairwise correlation value s is low ($s = 0.11$). Figure 9B shows that each neuronal type retains its own frequency, i.e., has its own typical ISI, separated from other neuronal types. We also notice that some neurons fire with low frequencies (5Hz) and others with higher frequencies (20Hz). Very low firing neurons (2Hz) which are typical for cortex are not represented in this model.

Next we changed the topology of the network to a graph with a lognormal distribution of connections (LG1), as shown in Figure 8. It used the same neurons ($N = 210$) and approximately the same number of excitatory connections $K = 1924$ as before.

Figure 7B shows an excerpt of the lognormal graph structure from LG1. The connectivity structure seems much denser, because of 'hub' neurons in the center of the graph. In Figure 8,

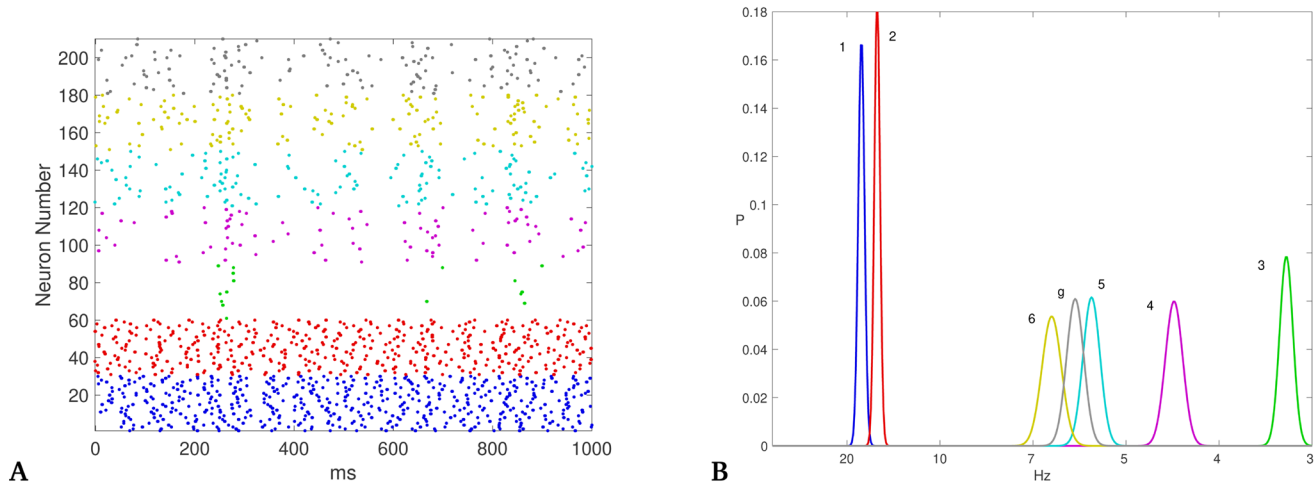


Figure 9. A. Asynchronous behavior in the Gaussian graph (RG) with variable neuron types. Groups of neuronal types with 30 neurons each are apparent in the rasterplot. Some structure is probably due to background inhibition. **B.** Average spikes/s with probability distributions for all neuronal types, with clear separation by frequency. Pairwise correlation is $s = 0.11$.

we can see the wider distribution of degrees for the lognormal graph (blue), containing a number of nodes with high connectivity ('heavy-tailed distribution'). Presumably, those nodes are capable of synchronizing the network, because they can reach many neurons simultaneously. What is the effect on the presence of neural heterogeneity?

Figure 10 shows that a high amount of synchronization can be achieved in spite of heterogeneity of intrinsic frequency of model neurons. The rasterplot (Figure 10A) shows the activity in LG1 with the same neurons and the same stimulation as before. The overall correlation, defined by pairwise correlation of neurons, is much higher ($s=0.32$). The distribution of ISIs in this case is strongly overlapping (Figure 10B), similar to Figure 4B, where neurons were explicitly driven by highly synchronous input. This means that synchronization is dependent on the network topology, and a lognormal graph exhibits a higher tendency for pairwise synchronization. Also, that neuronal heterogeneity is apparent in an asynchronous network mode but is repressed in a synchronous firing mode.

Dependence of synchronization on graph properties

We could show that differences in intrinsic properties appear or become more prominent when there is less synchronicity in a network. In our model, the pairwise synchronicity s is dominated by the network topology, more precisely by the width of the degree distribution ranging from Gaussian to lognormal.

To confirm this observation we used a number of intermediate graphs and mapped the pairwise synchronization dependent on the degree distribution width σ^* (Figure 11). The graphs RG and LG1 that we used have values of $\sigma^* = 1.44$ and $\sigma^* = 2.89$ (Methods). They have the same density, i.e., the same number of connections and neurons ($\bar{0}.05$). Additionally, we analyzed the

dependence of synchronicity on the density of the graph between 0.01 and 0.1 (Figure 11).

There is higher synchronization in the lognormal region, especially with $\sigma^* > 2.5$, but no synchronization for Gaussian graphs. For heavy-tail graphs, synchronization depends linearly on the density between $d = 0.03 - 0.08$ ($s = 0.2 - 0.5$).

How are the different graphs related? We hypothesized that fast synaptic switching²⁰ by neuromodulation could change the network topology sufficiently to switch from a synchronous to an asynchronous regime. In Figure 12, we plot the number of edges that were changed to achieve different distribution width σ^* of a graph. The algorithm used was a simple greedy algorithm (Methods), which is suboptimal, i.e., overestimates the number of edges required. It appears that 30–50% of edges changed would be sufficient.

Discussion

Network Topology, Synchronization and Intrinsic Read-out

We employ a parameterizable two-dimensional neural oscillator model to encode different intrinsic excitability manifested by different frequency responses to constant input. What the experiments show is that a stored intrinsic property, the gain, is available to the processing network in a conditional manner: the gain is continually present, the differences in ion channel density persist. Depending on the mode of stimulation, however, this property is manifested as spike rate, or it is obscured when a neuron is driven by strongly correlated input. This is interesting because it shows a property of memory that synaptic plasticity lacks: the memory is not always 'read-out' in any processing step. It is conditional, it can be accessed or ignored depending on the state of the network. This seems to be an essential property of memory in any intelligent system.

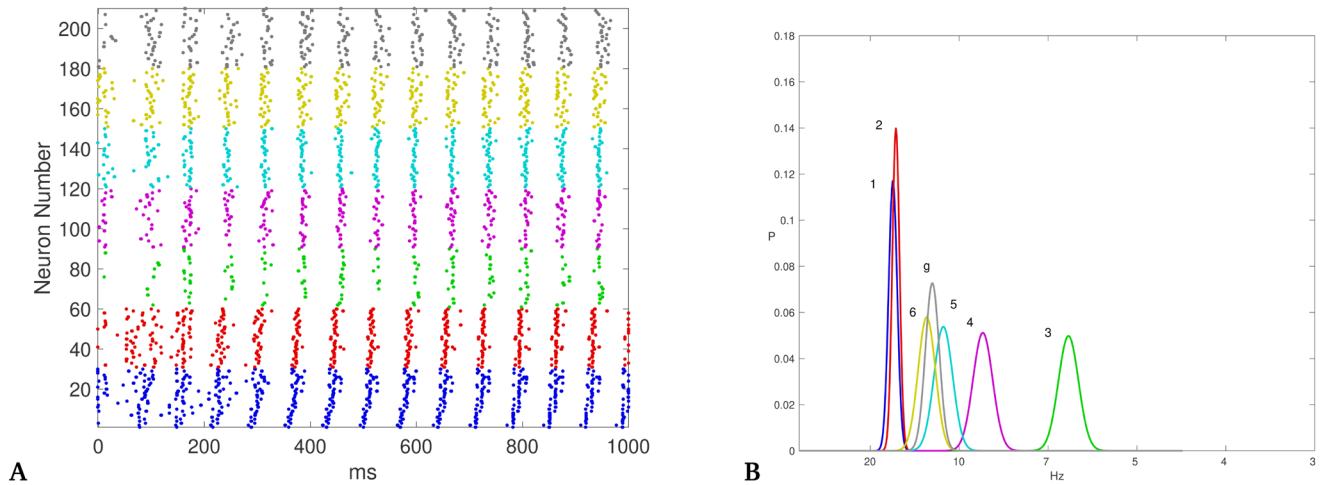


Figure 10. **A.** Synchronization in a lognormal graph (LG1) with variable neuron types. The rasterplot shows that different neuronal types respond uniformly. **B.** Frequency distributions. High overlap between neuronal types is apparent. Pairwise correlation in the graph is high with $s = 0.32$.

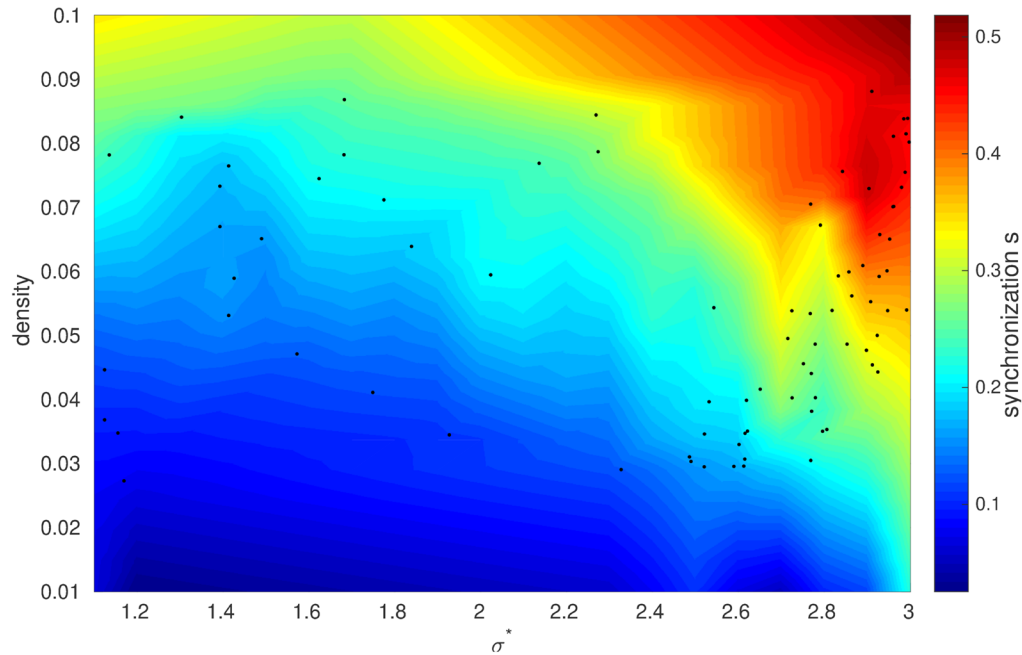


Figure 11. Synchronization s dependent on network topology: density and distribution width σ^* . The experimentally attested distribution width for weights in cortical tissue⁹ is $\sigma^* = 2 - 3.5$, with a mean at 3. We achieve higher synchronization s in the lognormal region, also dependent on density, but no synchronization in the Gaussian (region of low width) ($\sigma^* < 1.5$), except close to maximal connectivity. Black dots signify actual measurements. There seem to be no abrupt transitions.

Different statistical properties of synaptic input can be modeled by a variability in the correlation properties of input neurons. In a network model, this means that the overall correlation in the network determines what input a neuron receives. With a Gaussian degree distribution topology, correlation is low and neurons fire irregularly with their own preferred frequency. With a heavy-tailed, lognormal degree distribution topology, correlation is higher, and neurons fire when they receive correlated input,

irrespective of intrinsic properties. I.e., driving neurons by correlated vs. uncorrelated input leads to uniform spiking behavior vs. read-out of stored differences in ion channel conductances.

Inhibition

A restriction of the present model with respect to a biological simulation model is the simplified treatment of inhibition.

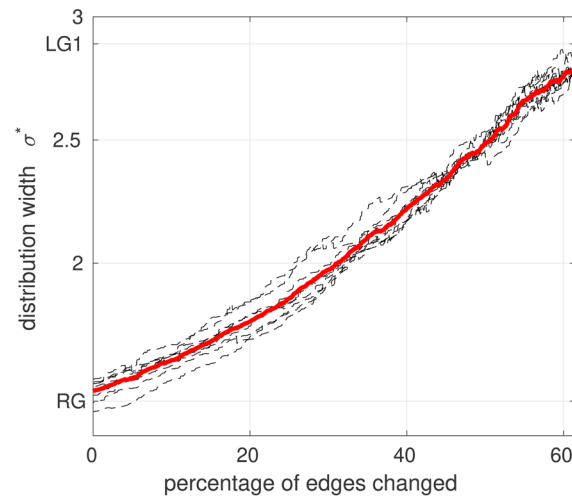


Figure 12. Transition between a lognormal graph and a Gaussian graph: For $K=1900$, $N=210$, $d=0.43$, mean over 10 trials, the percentage of edges changed to achieve a narrow degree distribution. The algorithm is not optimized (Methods) and overestimates the number of edges that have to be changed.

However, experimental work shows that cortical parvalbumin-expressing (PV+), fast-spiking interneurons have no connection specificity to pyramidal neurons, rather they present as an 'unspecific, densely homogeneous matrix covering all nearby pyramidal cells' (21, p. 13260), which corresponds to our model.

Conditions for neuronal read-out may include the activity of inhibitory neurons. Inhibition and excitation are tightly linked by feedback interaction. Graupner and Reyes (2013)²² suggested that the close coupling of inhibition and excitation in cortical tissue cancels out purely input-dependent, i.e. not network generated synchrony. Rudolph and Destexhe (2003)²³ suggested that with highly correlated input, both inhibitory and excitatory, the neuron may receive less input which allows it to be driven only by strong synaptic input, while distributed input consists of a barrage of excitatory and inhibitory inputs where the membrane voltage remains close to firing threshold and the neuron fires continuously. In our sense, it is 'reading out' its stored intrinsic frequency. Inhibitory and excitatory synaptic input conform to be either asynchronous or synchronous, to drive neurons by correlated input or to cause them to emit spikes according to their own intrinsic frequency.

However, neuromodulation has effects on inhibitory neurons as well^{24,25}, which we have not modeled. Further simulations will show whether the I-E coupling is altered during enhanced neuromodulation, or whether the effects are synergistic with the present results.

The role of neuromodulation

Neuromodulation influences both intrinsic properties and synaptic connectivity⁵, e.g., acetylcholine, (via nucleus basalis stimulation), noradrenaline (via LC stimulation) or dopamine (via VTA stimulation)^{5,26}. Experimental estimates on the distribution of synaptic neuromodulatory receptors are at approximately 30%–50% of connections²⁰. That is sufficient to transform the topological properties of a graph, such as the width of its

degree distribution from heavy-tailed graph to a more Gaussian, less clustered graph without requiring tight optimization for the positions of neuromodulatory receptors (Figure 12). Neuromodulation disables or enhances various ion channels, such as Sk-channels which guide reset times after a spike, or A-type potassium channels which influence latency to spike^{6,27,28}. In this way, neuromodulation influences intrinsic properties²⁹. If neuromodulation reduces synchrony by acting at synaptic receptors, it uncovers intrinsic heterogeneity, and induces a mode of processing that allows read-out and storing of intrinsic properties. Depending on the neuromodulator used, and the amplitude and duration of the signal, different somadendritic ion channel profiles would emerge^{30,31}.

In the synchronous mode, intrinsic heterogeneities are reduced in the presence of tightly correlated input which drives neurons reliably. This invariance of neuronal intrinsic properties in synchronous mode allows synaptic transmission and information processing independent of neuronal heterogeneity.

The idea of introducing synchronous events by common input to an asynchronous background, and in this way use reliable synaptic transmission without affecting the state of the system (multiplexing) has also been documented in experimental results. For instance, (Gutnisky *et al.*, 2017³², Figure 4A) shows a case of multiplexing in response to behavioral stimuli. In this case, intrinsic read-out can continue, and single events are transmitted reliably through driven activations.

Why should synchronization properties be switched by neuromodulation? Increased correlation in the network supports population-coded information to be propagated effectively³³. Turning on neuromodulation would decorrelate an area and increase the capacity for information coding in an ensemble or a cortical microcolumn³⁴. This area would become an information source to surrounding areas. When turned off, increased

correlation would allow this area to transmit information and to disregard the stored neural memory.

Relation to experimental evidence

Basal forebrain stimulation, which results in increased acetylcholine release and muscarinic/nicotinic receptor activation, decreases correlation between cortical neurons (35–37 (Figure 3.C)). Likewise, (Minces *et al.*, 2017³⁸, Figure 3 and Figure 4) shows reduced noise (internal) correlations with cholinergic stimulation, while inactivation of the basal forebrain caused more synchronized activity. Jeanne *et al.*, 2013³⁹ shows reduction of correlation for task-relevant perception, where presumably task-relevance causes neuromodulatory activity. Fazlali *et al.*, 2016⁴⁰ provides evidence for the involvement of noradrenaline in desynchronization of cortical state and the enhancement of sensory coding.

There is considerable evidence^{41–44} showing that several neuromodulators, including at least noradrenaline and acetylcholine, modulate pairwise spike correlation, such that strongly synchronized states (anesthesia, slow wave sleep) have high correlation and low neuromodulation, while asynchronous states (normal waking), with higher neuromodulation, have lower pairwise correlation.

Beaman *et al.*, 2014⁴⁴ observed intrinsic fluctuations in synchronization of cortical networks during wakefulness which correlated with the amount of encoded perceptual information and perceptual performance. Their results showed a mean decrease in correlations from synchronized to desynchronized state corresponding to perceptual performance by approximately 20%, similar to values observed during attention⁴⁵, and after adaptation⁴⁶. We have shown (Figure 11) that correlation changes are continuous with network topology and a 20% correlation change is well within the range of the current simulations. Importantly, the results in Beaman *et al.*, 2014⁴⁴ point to fluctuations in synchronization that reflect local changes in network activity rather than just global cortical state dynamics which have traditionally been associated with central neuromodulatory release.

The role of presynaptic neuromodulation in suppressing cortical connections^{11,12} and changing attractor states⁴⁷, as well as allowing rapid synaptic weight changes²⁰ has previously been assessed. Theoretical work has also emphasized the connection between correlations and information content^{34,48–50}.

Here we bring these observations together to suggest that neuromodulation of synapses may alter network topology and in this way bring about an increased decorrelation of spiking,

and a more asynchronous state, with a higher informational capacity. It may provide a general explanation (a) on how fluctuations in synchrony can be engineered rapidly and in small cortical areas and (b) why intrinsic memory may be conditional, accessible only at certain times and in a localized fashion.

Conclusion

We created a number of different parameterized neuron models to capture neuronal heterogeneity. This affects the properties of the neuron such that it has less or more intrinsic excitability, leading to different firing rates when stimulated in an asynchronous way. Under synchronous stimulation the differences are greatly reduced.

We also suggested that synaptic neuromodulation can be an effective way of rapidly altering network topology. We investigated changes in network topology along the dimensions of Gaussian vs. heavy-tailed degree distributions. We hypothesized that heavy-tailed graphs produce more globally synchronized behavior than comparable Gaussian graphs. In accordance with the hypothesis, we find that in a heavy-tailed graph, because of high population synchrony, the difference between neuronal intrinsic properties is minimized, while a Gaussian graph allows read-out of neuronal intrinsic properties. Thus, altering network topology can alter the balance between intrinsically determined vs. synaptically driven network activity.

Data availability

Underlying data for this study is available from Zenodo. Dataset 1. gscheler/CNeuroSyn: initial version, <https://doi.org/10.5281/zenodo.1164096>⁵¹.

Data is available under a Creative Commons CC BY-NC 4.0 license.

Software availability

The source code for the model is available from GitHub: <https://github.com/gscheler/CNeuroSyn/tree/V1.0/src/analysis>

Archived source code at time of publication is available from Zenodo <https://doi.org/10.5281/zenodo.1164096>⁵¹.

Software is available under GNU GPL v2.0 license.

Grant information

The author(s) declared that no grants were involved in supporting this work.

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Open Peer Review

Current Referee Status:



Version 2

Referee Report 15 March 2019

<https://doi.org/10.5256/f1000research.18791.r45036>



Jonathan P. Miller

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The authors of this paper sought to clarify how synaptic efficacy and intrinsic excitability of small-scale neural networks might be affected by neuromodulatory impulses. In a two-dimensional computational model simulating 210 excitatory cortical pyramidal neurons in a cortical microcolumn, they assessed spike synchronization under different conditions of network topology and density in order to assess the relationship of inputs and intrinsic excitability to output. They found that intrinsic network properties influenced output with asynchronous neuromodulatory inputs, whereas synchronous inputs were associated with driving of neural activity such that intrinsic properties disappear. The authors conclude that this effect may underlie flexibility of cortical computations, since the nature of inputs allows networks to shift between transmission and intrinsic readouts based on the synchrony of inputs.

Neural networks are known to have the ability to perform differently under different input conditions, allowing intrinsic information to be accessed or ignored depending on the state of the network, and this study provides insight into mechanisms underlying these processes. Notably, these observations are somewhat limited by the fact that they are based entirely on simulations with no confirmation in an actual experimental model, so there is a risk that the observed phenomena might be artifacts of assumptions used to build the model in the first place. The simulation is relatively simplistic, consisting of a small-scale model of exclusively excitatory neurons with excitatory connections driven by a single ion channel type. Nevertheless, this information suggests that the frequency specificity of synaptic neuromodulatory might affect synchrony of outputs as assessed by spike rates, and this has intriguing implications for informational capacity and conditional intrinsic memory.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Yes

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: neuroscience

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Referee Report 19 February 2019

<https://doi.org/10.5256/f1000research.18791.r43276>



Krešimir Josić

Department of Mathematics, University of Houston, Houston, TX, USA

I will not summarize the work again, as this was already done in the careful reviews of the first two referees. These referees have identified a number of issues that were only partially addressed in the current version of the manuscript. In particular, the generality and interpretation of the results, given that they are based solely on simulations, need to be addressed better, as pointed out earlier. Moreover, a number of relevant references are not discussed, and it is hence not possible to understand how the present manuscript complements the voluminous literature on the subject.

- The μ in Eq. 1 is a multiplicative factor, from what I gather from ref. 6. This is not clear.
- Why is σ in the exponent in the definition of σ^* ?

It is unclear that with $N = 210$ the effects of different degree distributions can be clearly observed. With this number of neurons finite size effects are likely still strong. In particular, the effects of a heavy-tailed distribution will likely only become apparent with more cells.

- The effects of driving neurons by synchronous input have been noted before, by Selinas and Sejnowski, and many others. As the previous reviewer points out, it is unclear what is different here. Similarly, the hypothesis that hub neurons can synchronize a population has been suggested before, eg. Bonifazi, et al *Science*, 2009¹, and many others.
- The currents in Figs 2A and 4B are nearly periodic. I would not expect this, unless they were generated using a mother process. In this case, the observation is actually a consequence of higher order correlations, ie. a common, synchronous input from many neurons that drive a response. Since it was unclear how the correlations in the inputs were generated, I could not tell if this was the case. However, this needs to be clearly explained.

The first two reviewers have made extensive comments. These were not addressed adequately. I believe these should be resolved before moving forward.

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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

Partly

If applicable, is the statistical analysis and its interpretation appropriate?

Partly

Are all the source data underlying the results available to ensure full reproducibility?

No

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: theoretical neuroscience

I have read this submission. I believe that I have an appropriate level of expertise to state that I do not consider it to be of an acceptable scientific standard, for reasons outlined above.

Referee Report 08 January 2019

<https://doi.org/10.5256/f1000research.18791.r41341>



Joel Zylberberg

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I appreciate the revisions, and I think that the new version is clearer and more complete than the previous one.

I still have a few minor concerns/suggestions: addressing these will, in my opinion, enhance the clarity and impact of this work.

- I still think it's important to mention in this paper (ideally in the Methods section) that the modelled synaptic inputs come from a current-based synapse model. That information is present in Ref. 6 of course, but it should be here for completeness. That way, without reading Ref. 6, readers will be able to understand why all the neurons (e.g., in Fig.1) get the same input current trace, even though they have different voltage time series: with conductance-based synapses, identical synaptic conductance inputs would lead to different current input time series.
- Some of the claims should be softened a bit, in my opinion. In so doing, they would be better supported by the data that's shown.

For example, in reference to Fig. 2 (p. 5): "We stimulate the same neurons with the correlated input and observe the spike pattern (Figure 2). We can show that the frequency-specificity of the neuron disappears." This isn't quite what the data show: the data show a strongly reduced difference in ISI distributions (vs. Fig. 1), but there is still a remaining difference. So it's not the case that the difference has

“disappeared”.

The same comment applies to the discussion of Fig. 5 (top of p.6): “the ISIs become identical, but with a wider distribution to reflect the different duration of pauses between the synchronous stimulation”. The ISI distributions shown in Fig. 5 are very similar, but they aren’t quite *identical*. So I’d suggest softening the language a bit in these places, to be more precise about what’s actually shown. I don’t think these changes much affect the conclusions of the paper, but they do make the text more accurate.

The discussion of Fig. 4 in the text is a good example of what I’m recommending: there, the distributions are described as *nearly* identical, which is a fair description at least for cells 1,2,4,5.

- Bottom of p. 8, “We now stimulate the graph by an initial stimulation to 10 randomly selected excitatory neurons (for about 1 second).” I still think it’s important to be clear about the protocol used for this stimulation. Was it with constant current injection? Was it with fluctuating current traces mimicking asynchronous inputs like in Fig. 1A, or with fluctuating current input mimicking synchronous input like in Fig. 2A? Moreover, was it the same current input for all neurons, or did they have different current inputs? Providing this information will give the reader context to understand and evaluate your methods, and the corresponding findings.

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Computational neuroscience, dynamical systems, sensory systems, memory, learning

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Version 1

Referee Report 24 October 2018

<https://doi.org/10.5256/f1000research.17251.r38207>



Guillaume Drion

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This paper compares (i) the response of heterogeneous neurons to two different types of synaptic inputs (uncorrelated or correlated), and (ii) the response of neuronal populations having two different types of synaptic weight distribution (Gaussian or Lognormal). The main results can be summarized as follows:

1. The chosen neuronal heterogeneity induces variability in mean spiking frequency. This variability persists under the application of uncorrelated synaptic inputs, but is masked by the application of correlated synaptic inputs.
2. Stimulating a subpopulation of neurons in a neuronal population induces an asynchronous response when the distribution of synaptic weights is Gaussian, whereas it induces a synchronous response when this distribution is Lognormal.

Then, it is speculated that switches between asynchronous and synchronous states can be controlled by neuromodulators, which would modify the network topology from Gaussian to Lognormal and conversely.

After carefully reading this paper, I think that neither the content nor the form is in a sufficiently advanced

stage for the manuscript to be indexed in its current form. A thorough revision is strongly suggested to boost the potential impact of the research. I provide specific comments below, in order of appearance in the text.

Table and figure captions are not descriptive enough. One cannot fully comprehend the different figures, which include numerous notations, by reading the captions. Some notations are not consistent (in Fig. 1-6, ISI is noted $I=^{***}$ on the left panels, and ISI on the right panels).

Title: The title is totally misleading. It states that “neuromodulation influences and intrinsic read-out”, but nothing of the sort is demonstrated in the manuscript. Neuromodulation is only speculated to be a plausible source to control the mechanisms highlighted in this manuscript, without any evidence or results to support this speculation. I have nothing against speculations and interpretations, quite the contrary, but they should not appear as grand truth in the title.

Abstract: The “Methods” part of the abstract is solely composed of results. This part should summarize the methods used in this paper.

Methods:

“For the experiments in this paper, we only focus on variability induced by changes in the strength of the slow A-type K channels. The total current contribution for this channel is μ As where μ was selected between 1.0 and 1.5.” Please motivate this choice (both channel type and chosen range), because the model is composed of 6 voltage-gated channels that could be used to model variability. Also, I would not use “experiments” but “simulations”, although this is a minor comment.

“Time-dependence is modeled by the gating variable u .” What does this sentence mean? Both ODEs model time-dependent evolution.

“By varying d , we can vary the inactivation dynamics of the model after a spike, by varying a we vary the inactivation dynamics throughout the computation.” I do not see the why variables a and d correspond to inactivations. a is the time constant of activation/deactivation of u (u indeed activates/deactivates, the slope b being always positive), and d is the increase in u after a reset, which represents how much a spike activates u .

*“For the excitatory neurons, we use randomly connected graphs (N,K) with different dispersion **sigma***. This corresponds to normal (Gaussian) to lognormal graphs with different widths and length of the heavy tail.”* This dispersion coefficient, and how it “corresponds to normal (Gaussian) to lognormal graphs with different widths and length of the heavy tail”, should be defined properly, because it is an important parameter in the results.

“The rewiring algorithm used to change the properties of a graph G is a greedy algorithm, which iteratively selects the node s with the highest degree”. Does “ s ” refer to a node, or is it a measure of network synchronization?

Results:

“We show how we can model gain as a stored intrinsic property, defined as a spike rate in response to constant or fluctuating input of fixed strength (A/Hz)” This sentence is unclear. What kind of gain is it referring to? What is a “stored” intrinsic property? What does “fixed strength” mean for a fluctuating input?

“In Figure 1A, we show the response of MSN model neurons with a scaling of $\mu IAs = 1.0, 1.3, 1.5$ to a noisy signal, derived from uncorrelated Poisson-distributed synaptic input.” From what I understood, neurons are not connected to each other in this case. It should be explicitly mentioned, because at this stage it is unclear whether we discuss isolated neurons or neurons within a network.

“The total number of spikes includes bursts, which were excluded from ISI calculation.” How were bursts defined? Why were they excluded from ISI calculation? But then why excluding them from one measure but not from the other?

Results related to Fig. 1 and 2: Only one example of uncorrelated/correlated input is shown, and conclusion is drawn from this example. This part requires further investigation. For instance, the increase in firing rate that we see in Fig. 2 could potentially induce overlapping of spiking rate, because it moves the neurons to a flatter portion of the f-I curve. It is important to rule out this effect to make sure that the difference is indeed due to the correlated/uncorrelated nature of the inputs, for instance by showing that increasing the firing rate with uncorrelated synaptic inputs does not induce the same effect. I also do not find surprising that inputs with high amplitude, low frequency fluctuations would affect the firing more than an almost constant input, but I guess that it is more subjective. You also talk about “a time-locked spike pattern”. How do you define it in the context of this paper? If it is synonymous of synchronization, having clearly separated frequencies does not mean neurons cannot be synchronized: one neuron could have a frequency that is twice the other and be fully synchronized, yet the frequencies would be separated. On the other hand, two neurons could fire at a same frequency and coefficient of variation, and yet not be synchronized.

“To continue with exploring this property of model neurons in a networked context, we switched to a simplified model neuron7 and created a set of variations for this model (see Methods).” Again, I guess that the results of this section are provided on isolated neurons. If it is the case, this sentence is misleading.

Results connected to Fig. 3, 4 and 5: My comment connects to the one relates to Fig. 1 and 2. The spikes of Fig. 3A look much more “time-locked” than the ones of Fig. 2A, although the conclusions that are drawn from these two figures are opposite. Is the “clear separation of ISIs” such a good measure in this context? In Fig. 4 and Fig. 5, most events look like bursts. Are bursts excluded from ISI calculation like in the previous case? If not why? Again, how is bursting defined in this case as compared to the previous case? Finally, in Fig. 5 all neurons seem to burst, yet the distribution of ISIs is a Gaussian, which does not make sense, unless you are only plotting the distribution for the interburst intervals.

“We first use a Gaussian connected graph (RG) with $N = 210$ and $K = 1800$ and use 7 different neuronal types (1–6, plus the generic neuron g) with 30 Neurons each (Methods). Figure 7A shows an excerpt of the graph structure. We can see that the graph is connected such that all neurons have a comparable number of connections. This is also apparent in Figure 8, where we can see a (narrow) normal distribution for connectivity for the Gaussian graph RG. Table 2 contains the graph characteristics for both graphs.” Only one graph is mentioned in the paragraph, and Table 2 shows 5 different cases. Both graph probably mean “Gaussian” and “Lognormal”, but that should be clarified.

“We now stimulate the graph by an initial stimulation to 10 excitatory neurons (for about 1s).” How were these 10 neurons selected? Where they selected randomly, or based on their degree of connectivity? Are they chosen to correspond to nodes with a high connectivity degree in the lognormal case? If so, then what is happening if we either stimulate neurons with lower connectivity degrees in the lognormal case, or add a few hub neurons in the Gaussian case? Is the difference in synchronization really due to the whole

distribution of the synaptic weights, or simply due to the existence of hub neurons that would be specifically targeted by synaptic inputs? This question needs to be answered in order to support the conclusion “*In our model, the pairwise synchronicity s is dominated by the network topology, more precisely by the width of the degree distribution (dispersion) ranging from Gaussian to lognormal with a heavy tail.*”

In Figure 11, are the “experimental conditions” similar than in Figures 9 and 10? Which 10 neurons are stimulated?

Discussion

“*Neuromodulation disables or enhances various ion channels, such as SK-channels which guide reset times after a spike, or A-type potassium channels which influence latency to spike.*” References that support these claims are needed.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

No

Competing Interests: No competing interests were disclosed.

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Referee Report 28 August 2018

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This study asks when the intrinsic biophysical properties of neurons do or do not affect their spiking responses to synaptic inputs. I denote the main claims and results of the paper as I,II,and III below, each of which is discussed individually thereafter.

I. The author begins by noting that, in the presence of strong synchronous inputs, essentially all neurons are driven to quickly spike, regardless of their intrinsic properties. In the presence of less-synchronous inputs, differences in intrinsic properties do lead to noticeable changes in spiking outputs. This is (presumably) because differences in integration time, and excitability (effective spiking threshold) determine how much input is needed to get the cell to spike, but sufficiently strong synchronous inputs always suffice to generate spikes. This is a neat observation, somewhat obvious in hindsight, but nevertheless made me glad to read the paper.

II. Next, they investigate how different network structures (quantified by dispersion of the graph's out-degree distribution) affect the synchrony in the inputs to individual neurons: networks with high dispersion (e.g., small numbers of critical "hubs" in the network) lead to higher synchrony. Thus, in those networks, the neurons' intrinsic properties are less influential than in networks with lower dispersion.

III. Finally, the authors speculate that, because neuromodulators can change effective connectivity, they could switch the network between different graph structures, thereby either enabling, or disabling, the influences of neurons' intrinsic properties. In that way, the network can "multiplex" between operational modes, one of which (the asynchronous one) is more affected by neurons' intrinsic plasticity, and thus more affected by memory and experience.

Below, I summarize first the relation to prior studies for each claim (I-III), and then comment on some technical and presentation issues that, to me, hinder somewhat the readability of the paper. My hope is that addressing these concerns will help the author to increase the impact of their work.

Comments on relation to other studies:

Result I. This is a neat observation. It is somewhat foreshadowed by some older work by Salinas and Sejnowski^{1,2}, showing that synchronous inputs are good at driving spikes in basically any neuron model. It would be useful to differentiate the findings of this paper from their older work.

Result II. Closely related results were obtained in a pair of studies by Yu Hu, James Trousdale, and colleagues^{3,4}. There, they computed the correlation structure (closely related to the author's synchrony measure) in networks with different connectivity motifs, using a neat analytical approach involving motif cumulants. It would be worthwhile (again) differentiating the results here from that prior work, so that readers know what's new and significant about this paper vs. the prior state of the field.

Result III. I'm puzzled by the claim that the network topology is strongly affected by neuromodulators (which is the key to the switching property that's discussed through the paper). While I understand that neuromodulators can strengthen or weaken synapses, that mechanism will change the weights within the graph describing network connectivity, but not change the underlying unweighted graph describing which neurons are connected to each other (regardless of the strength of that connection). To change the network topology, the neuromodulators would need to either a) add new synapses (or "unsilence" previously silenced synapses) selectively to some neurons, or b) remove (or completely silence) synapses selectively from some neurons. I think that, in order for the author to make claims about neuromodulators changing network topology, they should include some discussion (ideally based on the experimental literature) of when and how neuromodulators actually change network topology. This literature could of course exist: there's lots that I don't know about neuromodulators. And in that case, I think the author's claims would be much strengthened by referencing and discussing it.

Comments on presentation and specific technical issues:

1. Methods, 3rd paragraph. Why only focus on modulators affecting slow A-type K channels? Are those the most important ones? The ones most affected by common neuromodulators? Which neuromodulators are those?
2. Methods, 4th paragraph. It would help me if you would describe explicitly the method used to generate either correlated or uncorrelated synaptic input traces. For example, do these incoming spike trains (generating the synaptic inputs) come from a process like SIP or MIP? And specifically, how were the "correlation factors" quantified and manipulated?
3. Similar to (2) it would help to describe explicitly the synapse model used. For example, are the synapses conductance based (e.g., convolve incoming spike trains with a double exponential to get conductance traces)? I assume not, given that in Figs. 1-6, the same synaptic current trace is shown for all neurons. If the synapses were conductance-based, the differences in membrane potentials of those neurons would lead to differences in synaptic currents.
4. The definition of the synchronization is fine to me but doesn't seem to match the description in the preceding paragraph. Specifically, the formula doesn't seem to "count the number of other neurons which fire in a 10ms window. . ." so much as "count the number of spikes emitted by each other neuron in a 10 ms window".
5. I'd describe the rewiring process in the "graph properties" section of the Methods and not the "Definitions" section. That way, when you introduce the dispersion σ , you can explain the process used to manipulate it in your simulations.
6. The figures generally could use much more annotation, to help the readers parse what all the different curves mean. For example, in Figs. 1 and 2, I'd color code the curves (distributions) in panel B, and have those same colors used for the different spike trains in panel A, so that readers know which distribution goes with which spike train goes with which model. The same idea could be applied to the other figures: help the reader out so that, at a quick glance (which is how people read papers now) they can tell what's what and what the main point is.

Similarly, in Fig. 11, I'd label the color bar, so that people know what variable the colors are describing.
7. The formula for density on p. 6 (bottom left) seems incorrect, as $d=K/(N \times N-1)$. That would be $K/(N^2 - 1)$, whereas I think you mean $K/[N \times (N-1)]$.
8. P. 6, upper right, description of stimulating the graph by driving 10 excitatory neurons. How was this done? Did you inject current into those model neurons? If so, how much?
9. Some consistency between the network sizes in the simulations would help a lot. Specifically, in Fig. 10, you study a 1924 neuron network, whereas Fig. 9 uses 1800 neurons. This leaves the interpretation muddier than it needs to be: readers might wonder whether some of the differences could be attributed to changes in network size, and not just to changes in connectivity. In general, I'd suggest keeping all but one key variable constant, so that the comparisons can be made as cleanly as possible.

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2. Salinas E, Sejnowski TJ: Correlated neuronal activity and the flow of neural information. *Nat Rev Neurosci*. 2001; **2** (8): 539-50 [PubMed Abstract](#) | [Publisher Full Text](#)
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Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Partly

Are sufficient details of methods and analysis provided to allow replication by others?

No

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Computational neuroscience, dynamical systems, sensory systems, memory, learning

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

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