Statistical Fluctuations in Attractor Networks Related to Schizophrenia

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Abstract

We present a hypothesis of how the positive, negative, and cognitive symptoms of schizophrenia could be related to alterations in the stability of cortical networks which lead to a reduced signal-to-noise ratio. We analyze using integrate-and-fire simulations of attractor networks how some of the symptoms of schizophrenia could be related to a reduced depth of basins of attraction, produced by for example a decrease in the NMDA receptor conductances, and to statistical fluctuations caused by stochastic spike firing of neurons. Both of these processes contribute to instability in short term memory, attentional, and semantic neuronal networks. The cognitive symptoms such as distractibility, working memory deficits or poor attention could be caused by this instability of attractor states in prefrontal cortical networks. Lower firing rates are also produced, and in the orbitofrontal and anterior cingulate cortex could account for the negative symptoms including a reduction of emotions. If the decrease in NMDA conductances, and the statistical fluctuations, are combined with a reduction of GABA conductances, this causes the network to switch between the attractor states, and to jump from spontaneous activity into one of the attractors. We relate this to the positive symptoms of schizophrenia including delusions, paranoia, and hallucinations, which may arise because the basins of attraction are shallow and there is instability in temporal lobe semantic memory networks, leading thoughts to move too freely round the attractor energy landscape.

Introduction

Computational neuroscience utilizes a sophisticated repertoire of tools and models that describe various processes and functions of the brain [10]. Already in the early 1960 s, network models were developed to help understand perceptual processes [33]. More recent neural network models have also been applied to psychiatry [8, 20]. Recently Hoffman and MacGlashan [21] presented a network model that could simulate the auditory hallucinations that can be present in schizophrenia. Especially due to the relevance for patient treatment, the application of sophisticated models to psychiatric disorders is important, leading to a field which has been termed 'computational neuropsychiatry' [2]. Efforts are being made to develop this field in a systematic way [41]. Here we focus on a theoretical framework which addresses the symptoms of schizophrenia.

Schizophrenia is a major mental illness, which has a great impact on patients and their environment. The heterogeneity and complexity of the underlying biology make it difficult to develop detailed bottom-up theories, i.e. theories starting from the biological level which then attempt to account for the symptoms of schizophrenia. We propose a complementary top-down approach in which we consider the systems-level neural network changes that may contribute to the symptoms of schizophrenia, and then analyze the biological effects and changes that may contribute to the altered states of neural networks in the brain that appear to be related to the symptoms of schizophrenia.

In the following we use a dynamical systems framework to describe the altered neuronal network states that could be associated with the symptoms of schizophrenia. We aim to link the symptoms of schizophrenia and computational models of cortical function. Since the neurobiology of schizophrenia is heterogeneous and at

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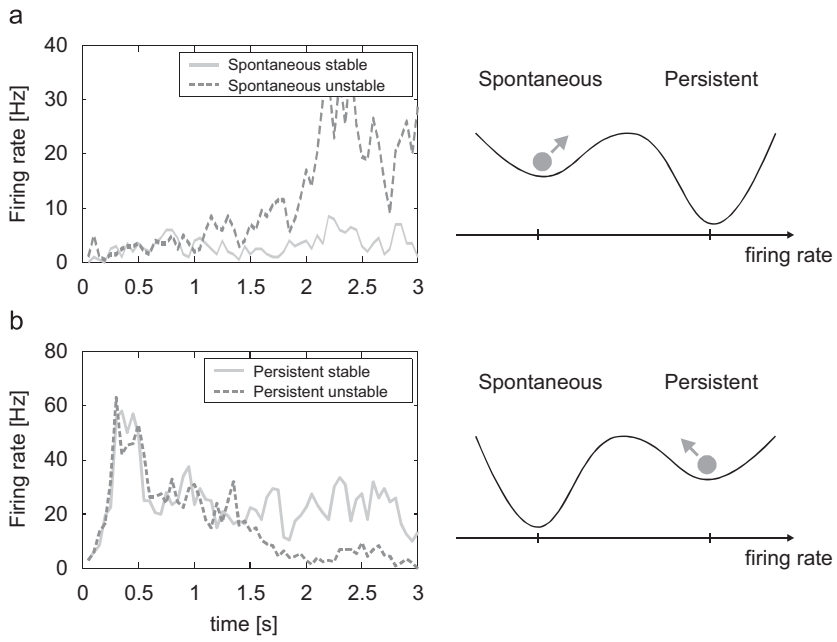

Fig. 1 **a**. Behavior of an attractor network during spontaneous state simulations. Left: Sample trials which are either stable or unstable. In the unstable spiking trial (dashed line), the firing rate escapes from the spontaneous attractor due to the influence of spiking-related statistical fluctuations. Right: The mechanism for escaping from the spontaneous attractor is pictured in a hypothetical energy landscape. We indicate for presentation purposes a ball jumping from the spontaneous state to the persistent state. The energy of each state is represented on the ordinate. **b**. Behavior of an attractor network during persistent state simulations. Left: The network is pushed into the persistent attractor state at the beginning, and due to the influence of statistical fluctuations the system leaves this state on some trials (dashed line). Right: This mechanism is pictured in the energy landscape as above.

times even inconsistent, there could be several biological mechanisms causing the characteristic symptoms of schizophrenia. Our approach may help to show how different biological changes could contribute to similar symptoms, and, importantly, may help to alleviate those symptoms.

Attractor framework

Our hypothesis is based on the concept of attractor dynamics such as those observed in autoassociation networks. These networks have an architecture typical of the cerebral cortex, with excitatory associatively modifiable recurrent collateral connections between nearby neurons [22,31]. These networks can maintain a stable pattern of firing of a subset of neurons that are strongly interconnected and form a memory pattern, and are thus useful for implementing short term memory, and thereby are important in maintaining attention. The whole of a memory pattern can be completed from a part, and thus these attractor networks are also useful in semantic memory.

In attractor networks, there are usually at least two distinct states: a spontaneous state marked by low neuronal firing rates, and a persistent state with higher firing rates in which one of the memory patterns is being maintained. Due to the influence of external inputs, or due to statistical fluctuations caused by the stochastical spiking of the neurons [38], the network can switch between these two states. That is, if the network is firing at a low rate, an external input can move the network to a persistent state at which it maintains a high level of firing rate representing one of the memories stored in the network even after the external input is removed (**Fig. 1a**). Fluctuations or external inputs can also switch the network back to a state of low, spontaneous, firing rate (**Fig. 1b**).

This behavior can be illustrated by an energy landscape [22]. **Fig. 1** shows such landscapes in which the attractor states (each one representing a memory) or fixed points of the network are indicated by the valleys. One can imagine a ball moving in that landscape which is at rest at the bottom of a valley. An extra force in terms of input or noise is needed to move the ball from one valley to another. In general, the hypothetical landscape can be multidimensional with several distinct attractor states each one representing a different stored memory. We envision that the brain as a dynamical system has characteristics of such an attractor system including statistical fluctuations.

The stability of the attractor and spontaneous states of the network can be measured by the strength of the input needed to move the system from one state to another. One factor important in the stability is the depth of the basins of attraction. The depth depends on the strength of the synaptic coupling between neurons. If the valleys or the depths of the basins of attraction are shallow as in **Fig. 2d** compared to **Fig. 2a**, then less force is needed to move a ball from one valley to the next. A second factor important in the stability is the noise in the system. High noise will make it more likely that the system will jump over an energy boundary from one state to another. Some of the noise in the system is due to the stochastical (probabilistic) spiking firing of neurons whereby spikes of a number of neurons can occur relatively close together in time (within e.g. 20 ms), and this source of noise can make the system move from one state to another, depending on whether these statistical fluctuations happen to influence especially the neurons that form one of the attractor states or the spontaneous state. (The timing of the spikes of cortical neurons is often quite random, and approximates a Poisson distribution.) The probability of moving from an attractor (i.e. persistent) state to the spontaneous state might be different from the probability of moving from the spontaneous to an attractor state (as illustrated in **Fig. 2b**). We note that there will in general be many attractor states, each corresponding to a memory, in an attractor network, so that under the conditions illustrated in **Fig. 2b** the system would move easily from one attractor state to another (with just one attractor basin shown in the diagram).

Our hypothesis builds upon the concept of shallow basins of attraction and contributes to an account of the different symptoms of schizophrenia [29]. At the core we argue that a changed attractor landscape together with the noise contributed by the

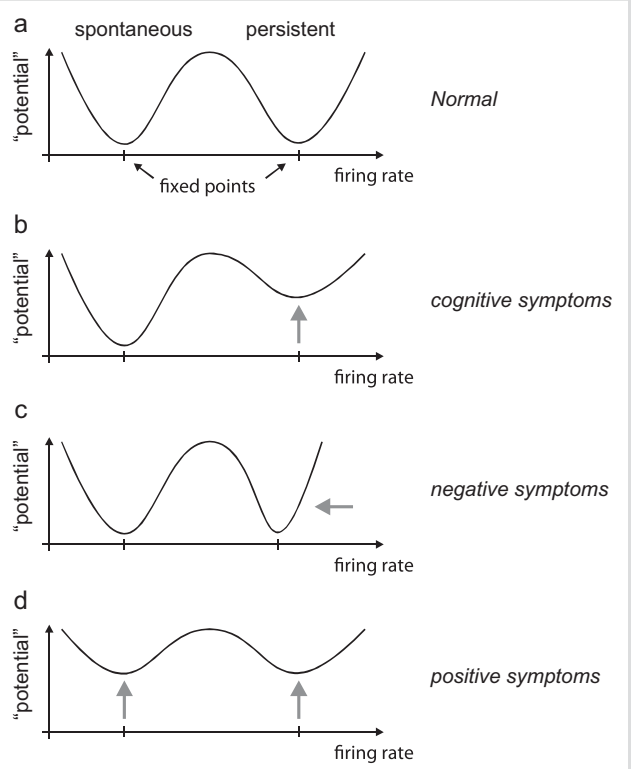

Fig. 2 Hypothetical energy landscapes of dynamical systems related to the symptoms of schizophrenia. The abscissa shows the firing rate, and the ordinate the hypothetical potential. The potential denotes the energy in terms of a dynamical system. It shows the energy needed to change the firing rates of the system. **a**. Unchanged, normal condition. The valley labelled persistent represents one of potentially very many different attractor or memory states. **b**. Cognitive symptoms might be caused by an instability of the working memory attractor states, which are also called persistent states featuring high firing rates. This instability is envisaged to be related to working memory deficits, in which the system moves easily from one attractor to another, because the depths of the basins of attraction are shallow. **c**. Negative symptoms are related to decreases in firing rate in the orbitofrontal cortex and/or anterior cingulate cortex. In standard attractor network models such as Hopfield networks or recurrent spiking networks as discussed here, a reduction of firing rate goes along with a shallower basin of attraction which results in a single mechanism for the cognitive and negative symptoms. **d**. Positive symptoms might result from shallow energy landscapes of the attractor and spontaneous states, which facilitate jumps between attractors and from the spontaneous state, in semantic memory systems in the temporal lobe. Part of the approach is that transitions between the states depend on statistical fluctuations caused by the stochastical spiking nature of the firing of the neurons in the network.

statistical spiking fluctuations causes an altered signal-to-noise ratio for the transitions between the different attractors and from the spontaneous firing state. The concept of an altered signal to noise ratio in schizophrenia is a concept of current interest [48], and we provide a dynamical attractor systems framework for analyzing how alterations in attractor networks might lead to an altered signal-to-noise ratio and to the symptoms of schizophrenia. We relate the three types of symptoms, cognitive dysfunction, negative symptoms, and positive symptoms [25,28], to the dynamical systems framework as follows.

Symptoms of schizophrenia

The cognitive symptoms of schizophrenia include distractibility, poor attention, and the dysexecutive syndrome [19,25,28]. The core of the cognitive symptoms is a working memory deficit in which there is a difficulty in maintaining items in short term memory [17,18]. We propose that these symptoms may be related to instabilities of persistent states in attractor neural networks caused by shallower basins of attraction, and thus a difficulty in maintaining a stable short term memory, normally the source of the bias in biased competition models of attention [13,31]. The shallower basins of attraction as illustrated in **Fig. 2b** would result in distractibility, poor attention, and working memory difficulties.

The negative symptoms refer to the flattening of affect and a reduction in emotion. Behavioural indicators are blunted affect, emotional and passive withdrawal, poor rapport, lack of spontaneity, motor retardation, and disturbance of volition [25,28]. We propose that these symptoms are related to decreases in firing rates in the orbitofrontal cortex and/or anterior cingulate cortex [29], where neuronal firing rates and activations in fMRI investigations are correlated with reward value and pleasure [29,30]. This is illustrated in **Fig. 2c** by a reduced firing rate of the fixed point of the persistent attractor. In standard neural attractor models such as the recurrent spiking network discussed in this article, a reduction in firing rate leads to a shallower basin of attraction. This unifies the cognitive and negative symptoms (**Figs. 2b,c**).

The positive symptoms of schizophrenia include bizarre (psychotic) trains of thoughts, hallucinations, and (paranoid) delusions [25,28]. We propose that these symptoms might result from a shallow energy landscape (**Fig. 2d**) in the temporal lobe semantic memory networks in which the attractor states are weak and the system jumps spontaneously between different persistent attractor states and also the spontaneous firing rate state. The thoughts wander loosely between weakly associated attractors, leading to bizarre associations, which may eventually over time be associated together in semantic memory to lead to false beliefs and delusions.

We emphasize that our hypothesis merely describes the effects in cortical networks and is not based on any biological cause or particular model, which might be described at several levels of abstraction in the brain. These range from the single neuron level up to systems neuroscience approaches [6]. The latter address complex networks often involving cortical and subcortical regions and including neuromodulators such as dopamine and serotonin which affect the dynamics of the interconnected levels in distinct ways. As schizophrenia is a heterogeneous disease, various biological causes could lead to the same set of symptoms and thus the hypothesized alterations in the dynamical attractor system. The overall goal is to investigate the pathways and mechanisms that lead to the hypothesized alterations, which can be done with various models describing effects at different levels. Here we analyse an attractor network which is a component of cortical microcircuitry, focusing on the contribution of NMDA and GABA receptor-activated synaptic currents.

Cortical microcircuit model

Our particular computational model uses a biologically realistic attractor neural network featuring an integrate-and-fire neuron

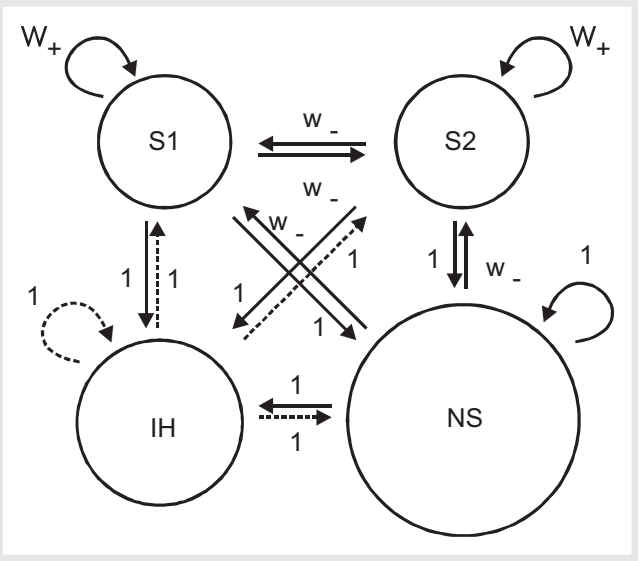

Fig. 3 The attractor network model. The excitatory neurons are divided into two selective pools or neuronal populations S1 and S2 (with 40 neurons each) with strong intra-pool connection strengths w_+, and one non-selective pool (NS) (with 320 neurons). The other connection strengths are 1 or weak w_-. The network contains 500 neurons, of which 400 are in the excitatory pools and 100 are in the inhibitory pool IH. The network also receives inputs from 800 external neurons, and these neurons increase their firing rates to apply a stimulus or a distractor to one of the pools S1 or S2.

implementation and synaptic channels for AMPA, NMDA and GABA*A* receptors [4]. These synaptic receptors are important since there is evidence that alterations in synaptic currents are related to the symptoms of schizophrenia [9,24], and many of the drugs used to treat schizophrenia act on these receptor-mediated currents, either directly or indirectly. Our model allows a detailed assessment of the stability of the system as influenced by the depth of the basins of attraction and the intrinsic noise of the system caused by the statistical spike-based fluctuations, which we suggest are related to the symptoms of schizophrenia.

The network contains 400 excitatory and 100 inhibitory neurons, which is consistent with the observed proportions of pyramidal cells and interneurons in the cerebral cortex [1,3]. The connection strengths are adjusted using meanfield analysis [4], so that the excitatory and inhibitory neurons exhibit a spontaneous firing rate of the spikes of each neuron of 3 Hz and 9 Hz, respectively [23,44]. The recurrent excitation mediated by the AMPA and NMDA receptors is dominated by the NMDA current to avoid instabilities during the delay periods [42].

The network structure, analogously to [4], contains two selective neuronal populations or pools, each of which represents a memory and can form an attractor state; together with one non-selective and an inhibitory pool of neurons (**Fig. 3**). The (associative) connection weights between the neurons of each pool or population are called the intra-pool connection strengths w_+. The strengthening of the intra-pool connections is counterbalanced by the other excitatory connections (w_-) to keep the average input constant. In addition, we include a non-selective pool in the model. For our investigations, we selected a parameter configuration for the strengths of the synapses, and for the NMDA and GABA currents introduced by each type of synapse into a neuron, which yielded a stable network that could maintain either of its attractor states, or the spontaneous state, stable depending on how the network was started. The parameter value $w_+ = 2.1$ yields the best trade off and therefore served as the baseline reference point. Details of the implementation used in this type of simulation are provided by [12] and [26].

The network receives Poisson input spikes via AMPA receptors which are envisioned to originate from 800 external neurons with an average spontaneous firing rate of 3 Hz from each external neuron, consistent with the spontaneous activity observed in the cerebral cortex [32,44]. Note that there are two sources of noise in such spiking networks: the randomly arriving external Poissonian spike trains, and the statistical fluctuations due to the spiking of the neurons within the network. These statistical fluctuations depend on the (finite) size of the network.

Our analysis is carried out by spiking simulations, which integrate the complete neuronal and synaptic dynamics over time including statistical components of the network model. We simulate the network for many trials with different random seeds and perform a statistical analysis on the data. We simulate two different conditions to assess the stability of both the spontaneous and the persistent states (see **Fig. 1**).

In spontaneous simulations, we run spiking simulations for 3 s without any additional external input. The aim of this condition is to test whether the network maintains a low average firing rate in the absence of any inputs, or whether it falls into one of its attractor states due to noise in the system (**Fig. 1a**) (which one could relate to hallucinations, intrusive thoughts, etc). In persistent simulations, an external cue of 120 Hz above the background firing rate of 2400 Hz is applied to each neuron in pool S1 during the first 500 ms to induce a high activity state, and then the system is run for another 2.5 s. The background firing rate of 2400 Hz can be viewed as originating from 800 external neurons firing at an average rate of 3 Hz per neuron. The aim of this condition is to investigate whether once in an attractor short term memory state, the network can maintain its activity stably, or whether it falls out of its attractor, which might correspond to an inability to maintain attention (**Fig. 1b**).

These two conditions are investigated with different changes made to the NMDA and GABA currents in the neurons, to investigate how modulations in these currents alter the behaviour of the network. For the NMDA and GABA modulations, we chose for demonstration purposes a reduction of 4.5% and 9%, respectively, from the baseline configuration. However, the exact values are not crucial for the effects that are found.

Stability and signal-to-noise ratio

We assessed how the stability of both the spontaneous and persistent states changes when NMDA and GABA efficacies are modulated. **Fig. 4** shows the percentage of sustained activities during spontaneous and persistent simulations. That is we assessed how often the system maintained the spontaneous or persistent state, assessed by the firing rate in the last second of the simulation (2–3 s) of each 3 s trial. This measures the stability of the system with no external distractor stimuli being applied. In the normal (unmodulated) condition, the spontaneous and persistent states are maintained in a high percentage of cases (around 90%). A reduction of the NMDA conductance (-NMDA) reduces the stability of the persistent state drastically, while slightly increasing the stability of the spontaneous state (see **Fig. 4**). We hypothesized that such a pattern might be

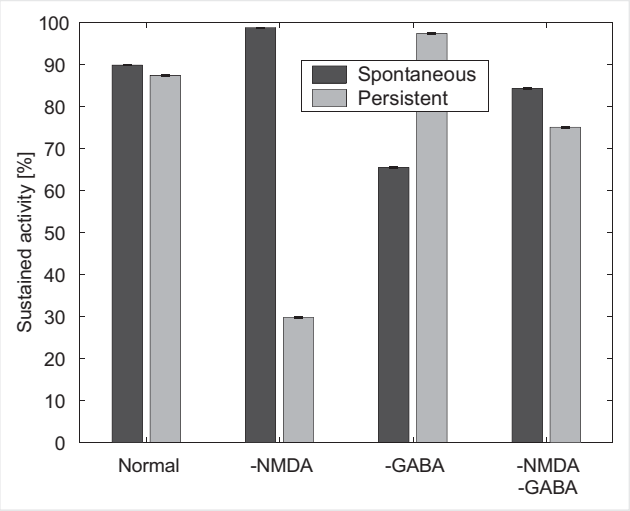

Fig. 4 Stability of the spontaneous and persistent state as a function of the modulations of the synaptic efficacies. We assessed how often in 1000 trials the average activity during the last second (2–3 s) stayed above 10 Hz. A modulation of the synaptic currents shown as -NMDA and -GABA corresponds to a reduction of 4.5 % and 9 % respectively in their efficacies. The sustained activity refers to the percentage in which the 1000 trials stayed in the respective state, i.e. a high activity (above 10 Hz) for the persistent simulations, and a low activity (below 10 Hz) for the spontaneous simulations. The standard deviations of the percentage of sustained activity (shown above each bar) were approximated with the binomial distribution and are below 0.1 % for all conditions.

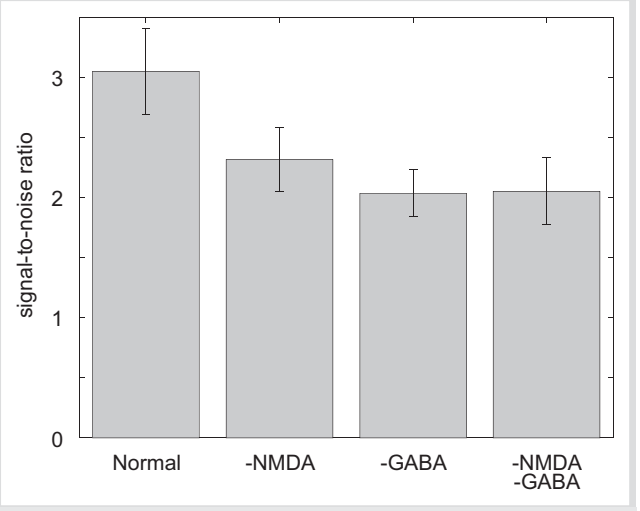

Fig. 5 Signal-to-noise ratio of a measure related to the BOLD signal as a function of the modulations of the synaptic efficacies. We computed the mean and standard deviation of averages of the synaptic currents of the selective pool over the whole simulation period of a persistent condition simulation. The mean of the spontaneous baseline condition was subtracted. We conducted 1000 simulated trials. The signal-to-noise ratio is calculated by division of the mean firing rate by the standard deviation measured using 1000 trials. The error bars indicate an estimation of the standard deviation measured over 20 epochs containing 50 trials each. A modulation of the synapses shown as -NMDA and -GABA corresponds to a reduction of 4.5 % and 9 % respectively in their conductances.

related to the cognitive symptoms, since it shows a reduced stability of the working memory properties (see **Fig. 2b**). (The core of the cognitive symptoms is a working memory deficit [17, 18].)

A reduction of GABA shows the opposite pattern: A slight reduction in the stability of the spontaneous state, and an increased stability of the persistent (i.e. attractor) state (see **Fig. 4**).

When both NMDA and GABA are reduced one might think that these two counterbalancing effects (excitatory and inhibitory) would either cancel each other out or yield a tradeoff between the stability of the spontaneous and persistent state. However, this is not the case. The stability of both the spontaneous and the persistent state is reduced (see **Fig. 4**). We relate this pattern to the positive symptoms of schizophrenia, in which both the spontaneous and attractor states are shallow, and the system merely jumps by the influence of statistical fluctuations between the different attractor states (**Fig. 2d**).

We relate the negative symptoms to a reduction of the mean firing rate of the persistent state of networks in for example the orbitofrontal cortex. A reduction of the firing rate was produced when the NMDA current was reduced (see also [4]). Thus, the cognitive and negative symptoms of our hypothesis can be related to the same synaptic mechanism, namely a reduction of NMDA conductance. An additional reduction of the GABA current leads to a change in activity of the network that models the positive symptoms according to our hypothesis.

We further investigated the signal-to-noise ratio in relation to the changes in synaptic conductances. The signal-to-noise ratio denotes the level of a signal relative to the level of background noise. In an attractor network, a high signal-to-noise ratio indicates that the network will maintain the attractor stably, as it will be unlikely to be disrupted by spiking-related statistical fluctuations that are the source of the noise in the network. High firing rates of the neurons in a persistent attractor state tend to make that attractor state stable due to the positive feedback between the neurons that form the attractor. Working memory implemented by the persistent attractor would tend to be stable and long-lasting if the signal-to-noise ratio is high. **Fig. 5** shows the signal-to-noise ratio of a measure related to the fMRI BOLD signal. We used the total synaptic current of selective pool 1 averaged over the whole simulation time of 3 s to take the filtering properties of the BOLD signal into account. Furthermore, we subtracted the averages of the spontaneous trial simulations which represent the baseline activity from the persistent trial simulation values. We envision that this measure is related to the fMRI BOLD signal. As shown in **Fig. 5**, we found that in all the cases in which the NMDA, or the GABA, conductance, or both, are reduced, the signal-to-noise ratio, computed by the mean divided by the standard deviation, is also reduced. This relates to recent experimental observations which show a decreased signal-to-noise ratio in schizophrenic patients [45, 47, 49]. Here we directly relate a decrease in the signal-to-noise ratio to changes (in this case decreases) in receptor activated synaptic channel conductances.

Overall, our approach shows that the cognitive and negative symptoms could be caused by the same synaptic mechanism, namely a reduction in the NMDA conductance, which reduces the stability of the persistent attractors, and reduces the firing rates of the neurons compared to the reference baseline condition. The positive symptoms could be accounted for in part by the same mechanism, namely a reduction of NMDA, but in addition reduction of the GABA conductance facilitates movement of the activity from the spontaneous state to a persistent state. This could be a mechanism that would, in the temporal lobe, lead to intrusive thoughts.

Dopamine

In our approach, we did not model dopamine specifically. We proposed a high level hypothesis of the symptoms of schizophrenia, and discussed its correlates in a neural network model in relation to NMDA and GABA synaptic conductances. The literature on dopamine is heterogeneous and multiple factors seem to determine the effects found. Dopamine itself might act in a highly complex network including cortical and sub-cortical regions. The utility of our approach is that it might describe the common pathway which leads to the symptoms of schizophrenia. There might be several causes which produce the proposed alterations of the attractor landscape, and alterations in the dopamine systems might be one of those.

The dopamine hypothesis of schizophrenia originally focused on a hyperdopaminergic state in the striatum partly due to the high density of D2 receptors [39]. In agreement with our hypothesis, newer versions of the dopamine hypothesis target the role of dopamine as altering the signal-to-noise ratio [48]. Frequent observation of abnormal frontal activations ('hypofrontality') in schizophrenia might be related to an increased instability in cortical circuits [45,49], which has also been indirectly related to dopamine [46].

Schizophrenia is treated with dopamine receptor D2 antagonists which mainly alleviate the positive symptoms, whereas the cognitive and negative symptoms persist, especially for the typical neuroleptics [28]. We found that the state corresponding to the positive symptoms (-NMDA, -GABA) and the one corresponding to the cognitive/negative symptoms (-NMDA) differ in the modulation of the GABA conductance. We reason that the net effect of neuroleptics might be an increase in the GABA conductance. This is also consistent with experimental work: it has been found that D2 receptors decrease the GABA contribution [34,40]. In a supersensitive D2 receptor state [36,37], D2 antagonists would increase the GABA currents and thereby increase the inhibition in the network. Increasing the inhibition in cortical microcircuits could be a therapeutic effect of D2 antagonists which would control the stability of the spontaneous state.

Although positive symptoms can be treated effectively in many patients, the negative and cognitive ones typically persist. To ameliorate the cognitive symptoms, the persistent state according to our hypothesis needs to be stabilized (see **Fig. 2b**). In the computational model investigated, the stability of the working memory state is linked to NMDA receptor mediated currents (see also [11,16,43]). A possible pathway to increase the NMDA currents could be via the D1 receptor [15,35].

Overall, we go beyond current approaches not only by connecting a dynamical systems framework to schizophrenia, but also by linking the cognitive and negative symptoms. That is, cognitive and negative symptoms could be treated by the same mechanism, namely an increase in NMDA currents. Newer medication might use this mechanism by increasing the NMDA current. D1 agonists are already being investigated as possible candidates [7,27]. There is also evidence that the cognitive symptoms worsen by medicating patients with D2 blockers [7]. In combination with the modeling results our hypothesis can account for this effect. If D2 antagonists indeed have the net effect of increasing inhibition in the network, our simulations suggest why cognitive symptoms worsen: the stability of the persistent state in the (-NMDA) condition is worse than the one in the (-NMDA, -GABA) condition (**Fig. 4**).

Our approach is different to some other modeling approaches in that we make a distinction between the different symptoms of schizophrenia and their specific mechanisms. Seamans et al. [34] have suggested two distinct states of dopamine modulation. One is a D2-receptor-dominated state in which there is weak gating and information can easily affect network activity. The other is a D1-receptor-dominated state in which network activity is stable and maintained (see also [14]). Since D2 antagonists do not restore the favorable balance as cognitive and negative symptoms persist, we suggested different mechanisms for the different symptoms. Most importantly, our simulations demonstrate that excitation and inhibition are not merely antagonistic as has been assumed in earlier approaches. They implement different functions in the network dynamics, and thus might be responsible for the distinct symptoms of schizophrenia, and the asymmetry in the treatments needed for the different symptoms.

Conclusions

The proposed alterations of the attractor landscape of brain activity could have a variety of causes: aberrant dopamine signaling, reduced neuropil, abnormalities in GABA and glutamate signaling, genetic mechanisms, and brain volume reduction [18,28,48]. Regional differences in cortical and subcortical regions and the different dopamine pathways including the mesolimbic and mesocortical pathways might also contribute to the causes [5,6]. Our neurodynamical hypothesis might serve as a unifying framework underlying the different physiological causes which all lead to the same instabilities in the attractor landscape as proposed for the schizophrenic symptoms. Since schizophrenia itself is defined by its symptoms, we believe that this approach is promising.

We investigated one possible cause, namely alterations in the NMDA and GABA conductances, in more detail. A reduction of NMDA can account for both cognitive and negative symptoms, which unifies these symptoms under one mechanism in this basic and therefore probably general model of an aspect of cortical function. Our results are consistent with experimental and modeling work on dopamine: We have shown what the net effects of dopamine on cortical microcircuits might be: D2 antagonists might act to increase GABA inhibitory currents and thus reduce the tendency of attractor systems to jump from the spontaneous firing state into an attractor; whereas facilitation of effects at the D1 receptor might increase the excitatory NMDA contribution and thus stabilize a high firing persistent attractor state once started. As an interesting modeling result, we demonstrate that inhibition and excitation are not merely antagonistic, but have distinct effects on the attractor landscape. A reduction of the NMDA and GABA contributions destabilizes the persistent attractor and spontaneous states respectively. This highlights the importance of the statistical fluctuations caused by the probability of spiking of neurons in the modeling of brain activity.

In schizophrenia, statistical fluctuations and signal-to-noise ratio seem to play a crucial role [48]. We show that a reduction in NMDA and GABA conductances leads to such a decrease in the signal-to-noise ratio (**Fig. 5**). A reduction in signal-to-noise ratio may be important in the dysfunctions of schizophrenia, and could have a variety of underlying causes. These could be investigated in statistical dynamical systems frameworks in relation to the alterations of the attractor landscape as proposed

here. We hope that our approach might help to deal with the heterogeneity and complexity of the neurobiology of schizophrenia by defining a common statistical dynamical framework based on the schizophrenic symptoms.

Acknowledgments

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