Computational models of schizophrenia and dopamine modulation in the prefrontal cortex

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Abstract | Computational neuroscience models can be used to understand the diminished stability and noisy neurodynamical behaviour of prefrontal cortex networks in schizophrenia. These neurodynamical properties can be captured by simulated neural networks with randomly spiking neurons that introduce noise into the system and produce trial-by-trial variation of postsynaptic potentials. Theoretical and experimental studies have aimed to understand schizophrenia in relation to noise and signal-to-noise ratio, which are promising concepts for understanding the symptoms that characterize this heterogeneous illness. Simulations of biologically realistic neural networks show how the functioning of NMDA (*N*-methyl-D-aspartate), GABA (γ-aminobutyric acid) and dopamine receptors is connected to the concepts of noise and variability, and to related neurophysiological findings and clinical symptoms in schizophrenia.

Dysexecutive syndrome
A disorder of the planning and organization of actions that is typically produced by damage to the prefrontal cortex.

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doi:10.1038/nrn2462

Schizophrenia is a major mental illness that has a great impact on patients and their environment. One of the difficulties in proposing models for schizophrenia is the complexity and heterogeneity of the illness. There are three main types of symptoms: cognitive, negative and positive. The cognitive symptoms of schizophrenia include distractibility, poor attention, working-memory deficits and the dysexecutive syndrome[1–3]. The negative symptoms include apathy, poor rapport, lack of spontaneity, motor retardation, disturbance of volition, blunted affect, and emotional withdrawal and passive behaviour[1,3]. The positive symptoms of schizophrenia include bizarre trains of thoughts, hallucinations and delusions[1,3]. Theoretical studies using neural-network simulations have started to address how this disorder can have such divergent symptoms.

Neural-network models have become increasingly sophisticated. Some current models include neurons with ion channels that open during synaptic activity, which involves particular types of excitatory and inhibitory receptors with biologically realistic time constants. The neurons in such models integrate the effects of the synaptic currents: if a threshold of depolarization is reached, they fire a spike that is transmitted to the synapses on the other neurons in the network. This 'integrate-and-fire' approach (and related approaches) allows the dynamical properties and the stability of the whole neural network to be investigated[4–7]. For example, researchers can investigate the effects of alterations in ion channels (for instance, in the currents that they pass) on the operation of the whole neural network in, for example, maintaining a short-term memory[7–9], maintaining attention and initiating action[10–12], or in decision making[13–16]. Given that the cognitive symptoms of schizophrenia include changes in these types of behaviour, these neural-network models are potentially useful in trying to understand the symptoms of schizophrenia.

In this Review we show how attractor networks are important for short-term memory and attention, and then how the random firing of neurons can influence the stability of these networks by introducing stochastic noise. We show how some of the different clinical symptoms of schizophrenia could be related to changes in the stability of such networks. Reduced stability of attractor networks can produce a reduced signal-to-noise ratio — for example, when a short-term memory is not always maintained and so the performance is unpredictable and, in this sense, noisy. We relate this to the concept that there is a reduced cortical signal-to-noise ratio in schizophrenia[17,18]. We then consider how alterations in dopamine in the prefrontal cortex could influence the stability and, thus, the signal-to-noise ratio of attractor networks in the prefrontal cortex and thereby produce some of the cognitive symptoms of schizophrenia.

Time constant
The time the system takes to reach 1/e of its initial value.

Attractor networks for short-term memory

An attractor network is a network of neurons with excitatory connections that can settle into a stable pattern of firing. In this section we describe how attractor networks operate in the prefrontal cortex and contribute to short-term memory and attention.

Pyramidal neurons in the cerebral cortex have a relatively high density of excitatory connections to each other within a local area of 1–3 mm[19,20]. These local recurrent collateral excitatory connections provide a positive-feedback mechanism (which is kept under control by GABA (γ-aminobutyric acid) inhibitory interneurons) that enables a set of neurons to maintain their activity for many seconds in order to implement a short-term memory[21]. Each memory is formed by the set of neurons in the local cortical network that was active when the memory was formed. The formation of a memory involves a strengthening of the excitatory connections between that set of neurons through the process of long-term potentiation. When a subset of these neurons is subsequently activated, positive feedback through the strengthened excitatory connections between the neurons results in activation of the whole set of neurons (a process known as pattern completion), and thus the entire memory is retrieved from just a partial stimulus. Thus, in an attractor network the state of the network is 'attracted' towards the state in which the memory was learned; this is called an attractor state. An attractor network can have many different attractor states, each consisting of a different set of active neurons; any particular set of neurons can represent a short-term memory. The operation and properties of attractor networks are described in BOX 1 and more fully elsewhere[16,22–25].

Attractor networks seem to operate in the prefrontal cortex, an area that is important in attention and short-term memory — as shown, for example, by neuronal firing in this area during the delay period of a short-term memory task[16,26–31]. Short-term memory is the ability to hold information online during a short time period[27,31]; it is fundamental to top-down attention in the sense that whatever requires attention (for example, a spatial location) has to be maintained in a short-term memory. The short-term memory then biases competition between the multiple bottom-up items in the stimulus input; as a result, in the neuronal competition between the multiple inputs, the item that receives top-down bias from the short-term memory has an advantage[22,32,33].The impairments of attention that are induced by damage to the prefrontal cortex might in large part be accounted for by an impairment in the ability to hold the object of attention stably and without distraction in the prefrontal cortex's short-term memory systems[16,26,34]. Specific simulations of impairments in the operation of prefrontal attractor networks can help to explain how the cognitive symptoms of schizophrenia, including poor short-term memory, poor ability to allocate and maintain attention, and distractibility, occur[35–38].

Stability of attractor states

BOX 2 shows how it is possible to model, using an integrate-and-fire approach, the individual neurons, synapses and ion channels that comprise an attractor network. This model can then be applied to the prefrontal cortex and used to link low-level neuronal properties to the short-term memories that result from the interactions between thousands of neurons in the whole network. In order to maintain a short-term memory, these interactions have to remain stable, and several factors influence the stability of such a short-term-memory attractor state.

Box 1 | Attractor framework

The attractor framework is based on dynamical-systems theory. In a network of interconnected neurons, a pattern (or set of active neurons) can be formed by synaptic modification and can be activated by external inputs. Furthermore, a pattern that is activated by an input is then stably maintained by the system even after the input ceases. These patterns could correspond to memories, perceptual representations or thoughts.

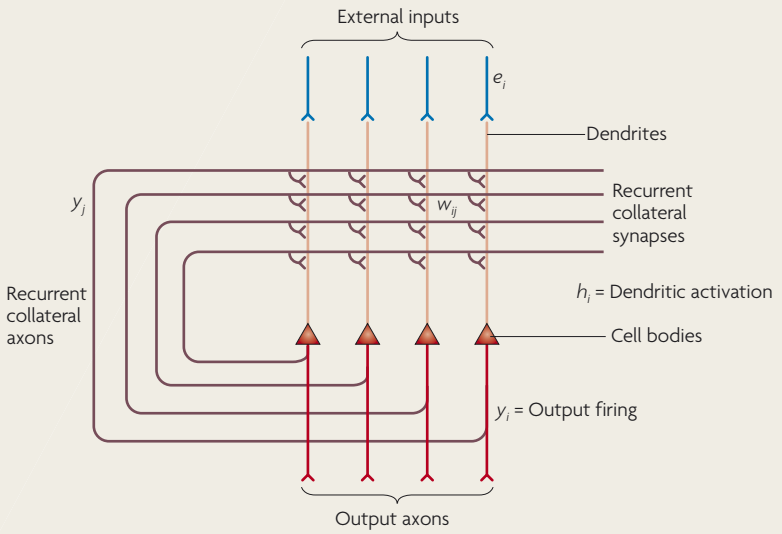
The architecture of an attractor (or 'autoassociation') network is as follows (see figure): external inputs (e_i) activate the neurons in the network and produce firing y_i, where i refers to the ith neuron. The neurons are connected by recurrent collateral synapses (w_{ij}, where j refers to the jth synapse on a neuron). Through these synapses an input pattern on e_i is associated with itself — that is why these networks are also referred to as autoassociation networks. Because there is positive feedback through the recurrent collateral connections, the network can sustain persistent firing. These synaptic connections are assumed to build-up through an associative (Hebbian) learning mechanism[133] (according to which, the more two neurons are simultaneously active, the stronger the neural connection between them becomes). Inhibitory interneurons are also part of this network (not shown in the figure). They receive inputs from the pyramidal cells and make negative-feedback connections onto them to control their activity.

The recall state (which could be used to implement short-term memory or memory recall) in an attractor network can be thought of as the local minimum in an energy landscape[23], where the energy would be defined as

$$E = -\frac{1}{2}\sum_{i,j} w_{ij}\,(y_i - \langle y \rangle)(y_j - \langle y \rangle)$$

where y_i is the firing of neuron i, and $\langle y \rangle$ indicates the average firing rate. The intuition here is that if both y_i and y_j are above their average rates and excite each other through a strong synapse, then the firing will tend to be stable and maintained, resulting in a low energy state that is stable.

Attractor systems have two types of stable, fixed points: a 'spontaneous' state with a low firing rate, and one or more 'persistent' states with high firing rates in which the neurons keep firing. Each one of the high-firing-rate attractor states can implement a different memory. When the system is moved to a position in the space by an external retrieval cue, it will move to the closest stable attractor state. The area in the space within which the system will move to a stable attractor state is called its basin of attraction.



Box 2 | Energy landscape and stochasticity

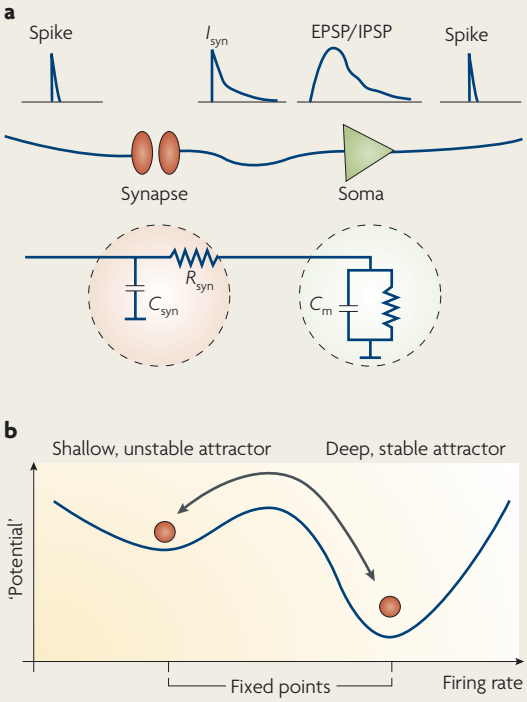
Realistic attractor-network architectures of the cerebral cortex (see BOX 1) are typically implemented by integrate-and-fire neurons and realistic synaptic dynamics[7] (see figure, part **a** and Supplementary information S1 (Box)). The integrate-and-fire model describes the subthreshold membrane potential, which is influenced by synaptic currents (see figure, part **a**):

$$C_m \frac{dV(t)}{dt} = -g_m(V(t)-V_L) - I_{syn}(t), \qquad I_{syn}(t) = g_s(V(t)-V_E)\sum_{j=1}^{N} w_{ij}s_j(t), \qquad \frac{ds_j(t)}{dt} = -\frac{ds_j(t)}{\tau} + \sum_k \delta(t-t_j^k)$$

where C_m is the membrane capacitance, g_m the leak conductance, $V(t)$ the membrane potential of the neuron, V_L the resting potential and $I_{syn}(t)$ the incoming synaptic currents. Here we just write one synaptic current $I_{syn}(t)$, where g_s is the synaptic conductance, V_E the current source, w_{ij} the synaptic weights and $s_j(t)$ the fractions of open synaptic channels. The synaptic variable $s_j(t)$ is described by an exponential decay that has time constant τ and is influenced by the incoming spikes k. When the threshold membrane potential V_{thr} is reached, the neuron is set to the reset potential V_{reset}. It is kept here for a refractory period t_{ref} and the action potential is propagated to the other neurons. These networks can maintain a set of neurons, which are strongly interconnected, in a stable firing pattern.

The attractor dynamics can be pictured by effective energy landscapes (see figure, part **b**), which represent the basin of attraction with valleys and the attractor states, or fixed points, with the bottoms of the valleys. The stability of an attractor is characterized by the average time in which the system stays in the basin of attraction under the influence of noise (which provokes transitions to other attractor states). Noise results from the interplay between the Poissonian character of the spikes (that is, the fact that the time at which each of a neuron's spikes occurs is random) and the finite-size effect that results from the limited numbers of neurons in the network. In fact, the number of spikes that is emitted by the network in a time interval dt is a Poisson variable with mean and variance $N\,r(t)\,dt$, where N is the number of neurons in the network and $r(t)$ is the average firing rate at time t. The estimate of $r(t)$ is then a stochastic process $r_N(t)$, which is well described in the limit of large N by $r_N(t) \cong r(t) + \sqrt{r(t)/N}\gamma$, where γ is Gaussian white noise with zero mean and unit variance and $r(t)$ is the probability of emitting a spike per unit time in the infinite network. Such finite-N fluctuations, which affect the global activity $r_N(t)$, are felt coherently by all neurons in the network.

Two factors determine the stability. First, if basins of attraction are shallow (as in the left valley in part **b** of the figure), less force is needed to move a ball from its current valley to the next. Second, a high level of noise increases the likelihood that the system will jump over an energy boundary from one state to another. We envision that the brain, as a dynamical system, has characteristics of such an attractor system, including statistical fluctuations. EPSP, excitatory postsynaptic potential; IPSP, inhibitory postsynaptic potential.



Attractor networks
Neural networks in which sets of neurons with strong interconnections have stable high-firing-rate states into which they can be attracted by memory-retrieval cues. The strong interconnections are formed during a learning period in which a set of neurons is active. An attractor net can be used to implement a short-term memory.

Long-term potentiation
(LTP). A long-term increase in synaptic strength.

Poissonian
With a Poisson distribution.

Hopfield equation
This is a measure of the stability of an attractor state that reflects the depth of the basin of attraction.

First, the stable states of the network are the 'low-energy' states in which one set of the neurons, connected by strengthened recurrent collateral synapses and representing one memory, is activated (BOX 1). The higher the firing rates of this set of neurons, the stronger will be the negative-feedback inhibition by the GABA inhibitory interneurons to the other excitatory (pyramidal) neurons in the network. This will keep the short-term-memory state stable, and will prevent distracting inputs to the other, inhibited, neurons in the network from taking over[7]. Any factor that reduces the currents through the NMDA (*N*-methyl-D-aspartate) receptors (NMDARs) on the pyramidal cells, as seems to occur in patients with schizophrenia[39], would decrease the firing rates of the set of activated neurons and tend to make the network more distractible[6,38].

Second, the strong synaptic connections that are implemented by the recurrent collateral synapses between the excitatory neurons in the network also tend to promote stability, by enhancing the firing of the neurons that are active during a particular short-term memory[40]. This helps to keep the energy low in the Hopfield equation (see the equation in BOX 1) and thus helps to make it difficult to jump from one energy minimum over a barrier to a different energy minimum that represents a different memory.

Third, the operation of the network is inherently noisy and probabilistic owing to the random spiking of individual neurons in the network and to the finite size of the network[41–45]. The random spiking will sometimes (that is, probabilistically) be large in neurons that are not among those in the currently active set; this chance

effect, perhaps in the presence of a distracting stimulus, might make the network jump over an energy barrier between memory states and into a different short-term memory, resulting in distraction. In a different scenario, the same type of stochastic noise could make the network jump from a spontaneous state of firing in which there is no item in short-term memory, to an active state in which one of the short-term memories becomes active. In the context of schizophrenia, this might represent an intrusive thought or hallucination. The effects of noise operating in this way would be more evident if the firing rates are low (and hence there is a low energy barrier over which to jump) or if the GABA inhibition is reduced (which, as post-mortem studies suggest, might be the case in patients with schizophrenia[46,47]), which would make the spontaneous firing state less stable. GABA interneurons normally inhibit the neurons that are not in the active set that represents a memory, but hypofunction of the NMDARs on GABA interneurons could diminish this inhibition[39].

Fourth, the stability of the attractor state is enhanced by the long time constants (~100 ms) of the NMDARs in the network[4,5,8,48]. The contribution of these long time constants (long in relation to those of AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) excitatory receptors, which are in the range of 5–10 ms) is to smooth out in time the statistical fluctuations that are caused by the random spiking of populations of neurons in the network, and thus to make the network more stable and less likely to jump to a different state. The different state might represent a different short-term memory, or the noise might return the active state back to the spontaneous level of firing, producing failure of the short-term memory and failure to maintain attention. Further, once a neuron is strongly depolarized, the voltage dependence of the NMDAR might tend to promote further firing[48]. If the NMDARs were less efficacious, as has been observed in patients with schizophrenia[39], the short-term-memory network would be less stable because the effective time constant of the whole network would be reduced owing to the greater relative contribution of the (short time-constant) AMPA receptors to the effects that are implemented through the recurrent collateral excitatory connections between the pyramidal cells[4,5,49].

Computational approaches to schizophrenia

Several computational models have been developed to investigate the symptoms that are associated with schizophrenia; they are described next.

Spurious attractor states. An early computational model by Hoffman included an attractor network. In this model some of the symptoms of schizophrenia could be explained by the effects of reducing the number of connections in an attractor network[50–52]: reducing the number of connections sometimes produced a memory state that was different from any particular memory that was stored in the network. These states were likely to occur if the retrieval cue that was used was not very similar to one of the stored memories, and if the reduction in the number of synapses on to each neuron reduced the capacity of the network[50] (so much so that it became close to the critical capacity of the attractor network, beyond which the network cannot usefully recall memories[23,24]). The resulting spurious attractor states were related to the positive symptoms of schizophrenia, such as intrusive and sometimes bizarre thoughts and delusions[50]. Although the neurons in these simulations were simplified neurons with binary firing rates (high or low), and although the spurious states that they produced can mainly be found with such simplified binary or saturating neuronal representations[53] (rather than with the graded representations that are found in the brain[16,22,54]), this approach has led to interesting insights into how disordered states in complex networks might contribute to psychotic symptoms. Hoffman and colleagues have further shown that pruning simulations of speech-perception networks that were trained with the artificial 'backpropagation of error' algorithm can result in spontaneous output (that is, output without input), and this was related to positive symptoms of schizophrenia, such as auditory hallucinations ('voices')[51,52,55]. Furthermore, reduced connectivity can lead to parts of a network operating as separate attractor networks[56,57], and this provides a model of the disconnection hypothesis of schizophrenia, in which, for example, the frontal and temporal lobes become relatively disconnected[58,59].

Connectionist models. In a different, connectionist approach, Cohen and collaborators have modelled some of the cognitive impairments that occur in schizophrenia[60–63]. Connectionist models are made up of computational units (FIG. 1a), in which the input, which originates from other units, is summed up through connection weights. The total input is then passed through a transfer or 'gain' function that typically has a sigmoid shape to produce the output (FIG. 1a). In their approach, it was suggested that the cognitive symptoms of schizophrenia might be caused by a failure of cognitive control, with 'cognitive control' referring to a process of actively maintaining task-relevant information in working memory to influence future operations[60–63]. An example of this approach is illustrated in FIG. 1b, which shows a model architecture used to simulate a continuous-performance task in which actions on the current trial require information from a previous trial to be held in working memory[61]. In this test, the participant has to respond to presentations of a letter A if it is followed, after a delay, by a letter X, whereas all other combinations (AY, BX and BY) are irrelevant. Thus, the task involves context processing: the A sets the context within which the following letter must be interpreted, and this requires stable but flexible working memory. In the model, dopamine multiplicatively altered the influence of the external inputs (A or B) on the working memory by affecting the gain function. If the gain was incorrect, then the A or B did not enter the working memory correctly and was not maintained until the next letter (X or Y) was presented. Schizophrenia was simulated in the model by increasing the noisiness (the variability) of the firing of the dopamine modulatory pathway and, as expected,

Disconnection hypothesis of schizophrenia
A hypothesis which suggests that brain regions such as the frontal and temporal lobes become relatively disconnected in schizophrenia.

Gain function
The sensitivity of a working-memory system to external stimuli in some models.

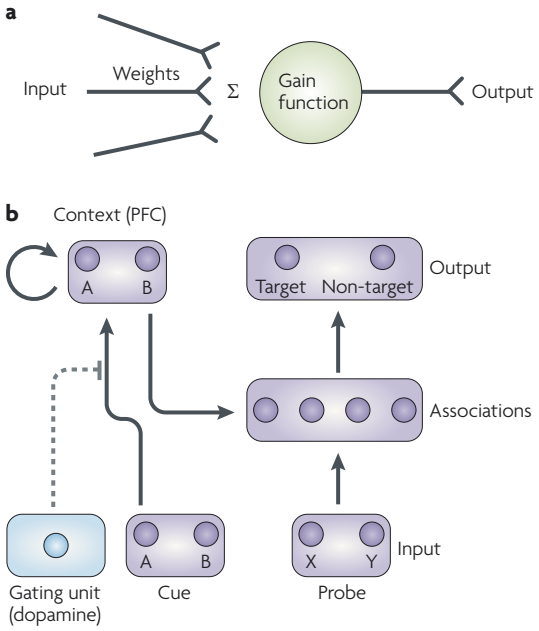


Figure 1 | **Connectionist models. a** | A typical connectionist unit, in which the inputs are weighted by connection weights, the result is summed by the unit and then a typically non-linear sigmoid-shaped 'gain' or transfer function is used to produce the output activity. **b** | A diagram of Braver, Barch and Cohen's connectionist model of the continuous-performance-task impairment in patients with schizophrenia. The context layer implements a short-term memory of whether an A or a B was shown on the preceding trial, and provides the association units with information about what was shown. The association units map the combination of the preceding 'A or B' input and the current 'X or Y' input to the output neurons by weights that are set by backpropagation-of-error learning. The change in performance that occurs in patients with schizophrenia is simulated by increasing the noise in the dopamine gating units, which determine whether the A or B inputs successfully drive the short-term context memory. The increased noise (or variability of dopamine firing) in the model causes the model to fail on some trials. Part **b** reproduced, with permission, from REF. 61 © (1999) Elsevier Science.

the short-term memory failed on some trials, resulting in poor task performance that was similar to that of patients with schizophrenia[61]. This type of modelling has the advantage that it can simulate the performance of particular tasks, and in future it might usefully be combined with more biologically realistic approaches that include synaptic channels, realistic time constants and spiking noise.

Integrate-and-fire and related models. Biologically more realistic models of neural circuits use, for example, integrate-and-fire or multi-compartment Hodgkin–Huxley neurons. This allows researchers to simulate in detail the influences of synaptically activated ion channels on the behaviour of the whole system. For example, Durstewitz and colleagues showed that dopamine-induced changes in ionic and synaptic currents, such as the persistent Na^+ current, the inactivating K^+ current, the high-voltage activated Ca^{2+} current, and NMDA and GABA synaptic currents, jointly influence the stability of activated representations (the 'memories') in an attractor network[9,64]. They focused on the effects of activation of the dopamine D1 receptor on the synaptic and neural channels in cortical regions (FIG. 2a). Their approach led to the suggestion that two states might exist in the prefrontal cortex: one state that is dominated by the activation of dopamine D2 receptors, in which attractor states are unstable but easily produced; and another state that is dominated by activation of D1 receptors, in which attractor states are stable and robust against distractions but are produced less easily by external inputs[65–67]. FIGURE 2b depicts these two states in an energy landscape. Two studies[65,68] have related this hypothesis to schizophrenia: the D2-dominated state might cause random or intrusive thoughts (positive symptoms) and working-memory deficits (cognitive symptoms), because it reflects a shallower attractor landscape; the D1-dominated state might reflect the narrowing of thoughts and attention as a result of the strong and stable maintenance of information (which the researchers related to the negative symptoms).

Synaptic currents, especially the NMDA currents, have received a lot of attention in computational modelling of working memory as they seem to be crucial for working-memory activity[4,8,49] and thereby are likely to have an important role in producing the cognitive symptoms of schizophrenia[69]. NMDA currents might be especially important for the stability of cortical attractor states, because their long time constants operate as a useful smoothing factor that decreases the destabilizing effects of random spiking noise in the network[4]. Conversely, NMDAR hypofunction could make cortical attractor states less stable by reducing the effective time constant of attractor networks, and in this way could contribute to the cognitive symptoms of schizophrenia[69]. D1 receptor activation might stabilize cortical attractor states at least in part by increasing the currents through NMDARs, which, by increasing the depth of the basins of attraction (BOX 2) and by increasing the effective time constant of the whole network, could make the network more stable. Thus, changes in the dopamine concentration might cause the cognitive deficits of schizophrenia by modulating NMDA currents.

In addition, inhibitory neurons in the cortex have recently received attention in computational modelling of working memory. Wang *et al.*[70] investigated a model that contained three different kinds of inhibitory neurons, namely calbindin-, calretinin- and parvalbumin-containing interneurons, with different characteristics and target neurons. The model revealed that a disinhibition mechanism is involved in filtering out distracting stimuli. Given the abnormalities in inhibitory circuits that have been associated with schizophrenia[71], this model might add another mechanism to the list of possible mechanisms for the enhanced distractibility in patients with schizophrenia. Overall, the balance between AMPA, NMDA and GABA currents seems to be crucial for the correct functioning of cortical circuits, and disturbances of this balance might have a wide range of consequences.

Multi-compartment Hodgkin–Huxley neurons
Models of neurons with separate biophysical parameters and modelling for the different parts of neurons, including different parts of the dendritic tree.

Basins of attraction
The shape in state space of the gradients of the low-energy, stable states into which a subset of neurons in an attractor network can be drawn.

A neurodynamical hypothesis of schizophrenia

The above models used bottom-up approaches that build on single-neuron biophysics and physiology and analyse their effects in neural networks, which are then linked to the symptoms of schizophrenia. A more recent, top-down approach considers whether a generic alteration that affects the operation and stability of cortical circuits in different cortical areas might lead to the different symptoms of schizophrenia[16,38,72,73]. This top-down approach complements the bottom-up approaches, because it starts from the set of symptoms and maps them onto a dynamical-systems framework. The dynamical-systems approach described earlier (BOX 2; Supplementary information S1 (box)) is a key part of the analysis. The analysis incorporates the contributions of NMDARs to the stability of cortical-network activity, in the context that NMDAR-hypofunction in the cortex is now known to be one of the key abnormalities in schizophrenia[39,74]. We build on the concepts of shallow basins of attraction (BOX 2) and noise introduced by the spiking dynamics, which together contribute to an account of the different symptoms of schizophrenia[38], and relate these to the concept of a reduced signal-to-noise ratio in schizophrenia[17,68,73]. We relate the three types of schizophrenia symptoms (cognitive deficits, negative symptoms and positive symptoms) in our top-down approach to the dynamical-systems framework as described below[16,38].

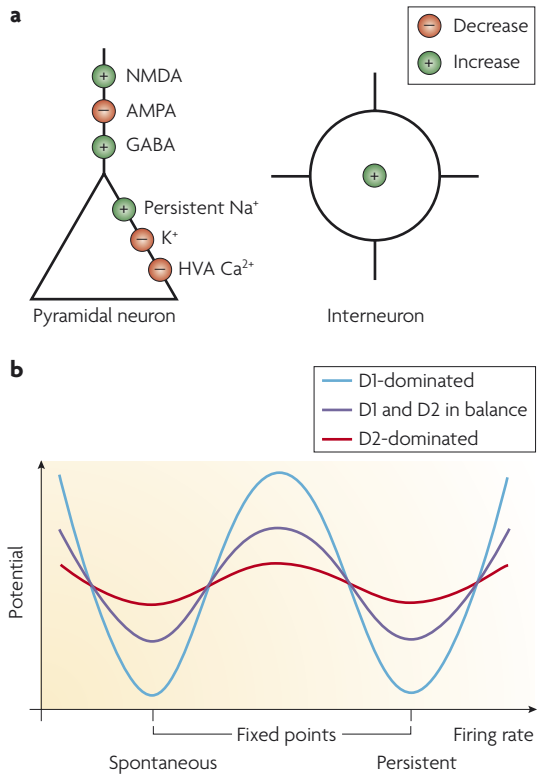


Figure 2 | **Dopamine effects in the prefrontal cortex.** **a** | A Hodgkin–Huxley-type model of the effects of dopamine D1 receptor activation on cortical pyramidal neurons and interneurons[9]. A higher dopamine concentration increases NMDA (*N*-methyl-D-aspartate), GABA (γ-aminobutyric acid) and persistent Na^+ currents and the activity of interneurons, whereas it decreases AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid), K^+ and high-voltage-activated (HVA) Ca^{2+} currents. **b** | Different concentrations of dopamine in the cortex might cause conditions in which the activation of different receptor types (dopamine D1 and dopamine D2) changes[66]. In the D1-dominated state the depth of the basins of attraction might deepen, whereas in a D2-dominated state the energy landscape might be flatter than normal. Part **a** reproduced, with permission, from REF. 77 © (2002) Pergamon Press and from REF. 65 © (2004) Pergamon Press. Part **b** reproduced, with permission, from REF. 129 © (2008) Elsevier Science.

Blood-oxygen-level-dependent (BOLD) brain response
A signal that can be extracted with fMRI and that reflects the change in the amount of deoxyhaemoglobin that is induced by changes in the activity of neurons and their synapses in a region of the brain. The signal thus reflects the activity in a local brain region.

Cognitive symptoms. The cognitive symptoms of schizophrenia include distractibility, poor attention and the dysexecutive syndrome[1–3]. It has been suggested that at the core of the cognitive symptoms of schizophrenia is a working-memory deficit that is characterized by a difficulty in maintaining items in short-term memory (a process that requires the dorsolateral prefrontal cortex)[75,76]. Building on work by Seamans and Yang[65], we propose that the working-memory deficit might be related to instabilities of the high-firing states in attractor networks in the prefrontal cortex (FIG. 3a). Specifically, NMDAR hypofunction, which has been associated with schizophrenia[39,74], results in reduced currents running through NMDAR-activated ion channels; this causes neurons to fire less fast, leading to shallower basins of attraction (BOX 2) in the high-firing-rate attractor states of the network[38]. Thus, the stability of the attractor state is reduced, resulting in difficulty in maintaining a short-term memory and, consequently, in difficulty in maintaining attention[66,77] (FIG. 3a). The shallower basins of attraction and the reduced time constant of the system caused by NMDAR-hypofunction[69], in the presence of the stochastic-firing-related noise in the networks, result in distractibility, poor attention and working-memory difficulties.

Negative symptoms. The negative symptoms are a complex of symptoms, including apathy, poor rapport, lack of spontaneity, motor retardation, disturbance of volition, blunted affect, and emotional withdrawal and passive behaviour[1,3]. The occurrence of negative symptoms and cognitive deficits is highly correlated both in patients with schizophrenia and in their non-psychotic relatives[78–80]. We propose that the negative symptoms are also related to the decreased firing rates that are caused by a reduction in the currents through NMDAR-activated channels, but in brain regions that might include the orbitofrontal cortex and the anterior cingulate cortex[16,72,81] rather than the prefrontal cortex. Indeed, lesions in these brain areas are well known to produce symptoms that resemble the negative symptoms of schizophrenia, and neuronal firing rates and blood-oxygen-level-dependent (BOLD) activations in these regions are correlated with reward value and pleasure[16,72,82–85]. This is a unifying approach to the cognitive and negative symptoms: the same reduction in NMDAR-activated channel currents produces on the

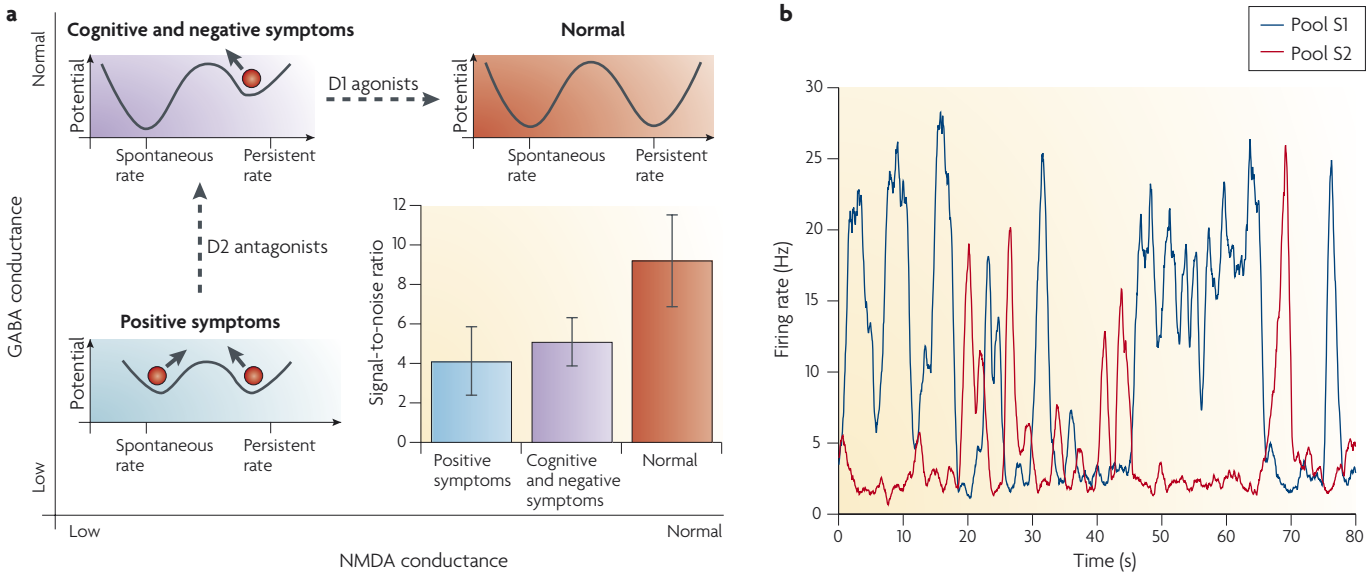


Figure 3 | **Attractor hypothesis of schizophrenia. a** | A hypothesis for the different types of symptoms of schizophrenia[38,73]. The cognitive symptoms (top left) are attributed to a reduction in the depths of the basins of attraction of the high-firing-rate, persistent attractor states (see BOX 2), which in prefrontal cortex networks makes short-term memory and attention unstable. The negative symptoms (also top left) are related to a concomitant decrease in the firing rates of neurons in the orbitofrontal and anterior cingulate cortices. The positive symptoms (bottom left) are related to a flat energy landscape in which both the spontaneous (low firing rate) and the persistent (high firing rate) attractor states are shallow in memory and perceptual networks in the temporal lobe. Simulations of an integrate-and-fire network show that reduced NMDA (*N*-methyl-D-aspartate) and GABA (γ-aminobutyric acid) activity can cause the types of changes in the attractor landscape[38] that are shown in this figure. The changes in signal-to-noise ratio that are associated with these changes in the basins of attraction are indicated in the bottom right panel[38]. The signal-to-noise ratio is reduced in both scenarios. Specifically, this bottom-right graph shows the signal-to-noise ratios in integrate-and-fire simulations that result from reductions of NMDA conductances by 5% (cognitive and negative symptoms) and from an additional reduction of GABA conductances by 10% (positive symptoms)[38]. The signal-to-noise ratio shown in the figure was calculated by squaring the mean synaptic currents and then dividing this value by the variance of the synaptic currents, a measure analogous to that used in EEG investigations on patients with schizophrenia[17]. For the synaptic currents, we used the difference between the currents of the persistent and spontaneous simulations (to account for the baseline) of the selective pool over the whole simulation period. We conducted 1,000 simulated trials. The error bars indicate an estimation of the standard deviation measured over 20 epochs containing 50 trials each. **b** | Wandering between attractor states. The graph shows the outcome of an integrate-and-fire simulation of an attractor network in which two memories (S1 and S2) are stored. With normal synaptic efficacies and no initial cue in the simulation, the network would stably stay in the spontaneous state, with little activity in the neurons in the S1 and S2 neuron pools. However, on trials of the type shown here, in which NMDA conductances were reduced by 5% and GABA conductances were reduced by 10%, the activity moves noisily between the attractor for the spontaneous state (low firing rate) and those for the two persistent states, S1 and S2 (high firing rates), by virtue of statistical fluctuations that are caused by the randomness of the spiking activity. The two curves show the activity of the two selective pools, S1 and S2, over time, smoothed with a 1 second sliding averaging window[38]. D1, dopamine D1 receptor; D2, dopamine D2 receptor.

one hand instability in high-firing-rate states in attractor networks in the dorsolateral prefrontal cortex and, thereby, the cognitive symptoms, and on the other hand a reduction in the firing rate of neurons in the orbitofrontal and cingulate cortices, leading to the negative symptoms. In addition, attractor networks that help to maintain mood state might be present in the orbitofrontal cortex[16], and a decrease in their stability resulting from a reduction in the depth of the basins of attraction could make emotions more labile in schizophrenia and schizoaffective disorder.

Positive symptoms. The positive symptoms of schizophrenia include bizarre trains of thoughts, hallucinations and delusions[1,3]. In contrast to cognitive and negative symptoms, positive symptoms generally occur intermittently during the course of the illness, and this clinical state is called 'psychosis'. We propose that in patients with schizophrenia the basins of attraction of the high-firing-rate attractor states are shallow[38,67], owing to reduced currents through NMDAR-activated channels in the temporal lobe, which includes the semantic-memory networks and the auditory-association cortex. Because of the resulting statistical fluctuations in the states of the attractor networks, internal representations of thoughts and perceptions move too freely around in the energy landscape — from thought to weakly associated thought — leading to bizarre thoughts and associations and to hallucinations (FIG. 3a). Such thoughts might eventually be associated together in semantic memory,

leading to false beliefs and delusions[16,72]. A reduction in GABA-interneuron efficacy in patients with schizophrenia might also contribute to the generation of positive symptoms: lower GABA-interneuron efficacy reduces the depth of the basin of attraction of the spontaneous state, making it more likely that a high-firing-rate attractor state will emerge out of the spontaneous firing of the neurons.

On the basis of this model, we propose that treating patients with schizophrenia with D2 antagonists could increase the GABA currents[65,86] in the networks; this would alleviate the positive symptoms by reducing the spontaneous firing rates, which would in turn deepen the spontaneous attractor state (FIG. 3a). This effect of D2 antagonists leaves the persistent attractors shallow because the high firing rates are reduced, which might explain why the D2 antagonists do not have a major effect on the negative and cognitive symptoms. To target negative symptoms, we suggest that D1 agonists might help to deepen the basin of attraction of the high-firing-rate attractor state. This two-dimensional approach allows us to address the specific characteristics of the psychotic (positive) symptoms, which appear in episodes, in contrast to the negative and cognitive symptoms, which typically persist over time.

When both NMDA and GABA are reduced, one might think that these two counterbalancing effects (excitatory and inhibitory) would cancel each other out. However, this is not the case (see also REFS 7,77): modelling these conditions showed that the stabilities of both the spontaneous and the high-firing-rate states are reduced[38]. Indeed, under these conditions the network wandered freely between the two short-term memory (high-firing-rate) states and the spontaneous state (FIG. 3b). We relate this pattern to the positive symptoms of schizophrenia, in which the basins of attraction of both the spontaneous and the high-firing-rate states are shallow, and in which the system jumps, with the aid of the statistical fluctuations, between the different attractor states and the spontaneous state[38] (FIG. 3a).

Importantly, in the computational models stability is defined as the proportion of trials on which the correct short-term memory (or signal) is maintained until the end of the trial, and the signal-to-noise ratio can be found by squaring the mean rate of firing and then dividing this value by the variance of the synaptic currents over the whole trial period[38,73]. The models highlight three possible mechanisms that could underlie a decreased signal-to-noise ratio, as reflected in reduced stability; these mechanisms could be relevant for the decreased signal-to-noise ratio that occurs in schizophrenia (see below). First, the reduction in NMDAR-activated synaptic currents will reduce the firing rates of neurons, and this will decrease the depth of the basins of attraction of cortical attractor states, making them less stable in the presence of spiking-related noise and other noise in the brain, and in the presence of distracting stimuli in the world. Second, the reduction in NMDAR-activated currents will reduce the time constant of the whole attractor network, also making the attractor states less stable in the presence of noise and distracting stimuli. Third, the reduction in GABA receptor (GABAR)-mediated currents might reduce the stability of the spontaneous state, and the resulting noise will cause the system to jump into a high-firing-rate attractor state, as described above[38,73].

Local field potentials
The potentials in a local brain area that reflect the activity of many neurons and their synaptic inputs.

Schizophrenia and noise

When relating clinical symptoms of schizophrenia to the dynamical network properties of cortical neurons, it is critical to obtain experimental evidence in support of this relationship. However, it is generally impossible to study, for instance, spiking neuron behaviour in patients with schizophrenia. What researchers can do is investigate electromagnetic fields, as obtained through electrophysiological scalp recordings (an electroencephalogram (EEG)), or conduct imaging experiments with functional MRI (fMRI). Here then we must explain how EEG and fMRI measurements are related to the behaviour of spiking neurons — in particular with regard to noise in spiking neurons. Although the field's understanding of this relationship is currently incomplete, recent research is shedding more light on the issue.

Measuring noise with EEG and fMRI. It is widely appreciated that the massive synaptic bombardment that neurons receive *in vivo* represents a strong source of noise[85]. A plot of signal-to-noise ratio as a function of noise intensity shows an inverted 'U' shape, with an optimal or 'resonant' noise amplitude at which the periodicity of the signal is maximal. This kind of noise-induced oscillation is observed in a wide range of nonlinear systems and is called coherence resonance. One study[85] compared coherence resonance in two major functional types of neurons in the cortex, namely regular-spiking pyramidal neurons (type 1) and fast-spiking interneurons (type 2). Coherence resonance of spiking activity was observed in both types of neurons — albeit in a wider range for type 2 neurons, which suggested that this physiological characteristic might explain the prominent role of interneurons in synchronizing the spiking activity between cortical neurons (see also REFS 87–89). As put forward by Friston[87–89], synchrony will provide a neural network with a transient stability that will keep the high-firing-rate (short-term memory) state stable, and will prevent distracting inputs to the other, inhibited neurons in the network from taking over[7]. (We note that information in the brain is carried by firing rate and, to some extent, by stimulus-dependent spike synchrony[16,22,80,90–92]; the relative contribution of these two codes is still a matter of investigation. Also, irregular interspike intervals are not necessarily stochastic: they can be predictable and correlated between neurons (for example, see REFS 93–95).) If (resonant) coherence (and spike synchrony between neurons) is low, the corresponding trial-by-trial variability of synaptic activity during a task will reduce the amplitude of local field potentials (LFPs). This is because LFPs reflect the temporal properties, including the synchrony, of synaptic activity across dendrites[96], and because spike synchrony and synaptically generated LFPs are closely related[90,97]. By extension, because LFPs give rise to electromagnetic fields[98], trial-by-trial variability of synaptic activity will influence the oscillatory

properties and the variability of these fields (that is, event-related potentials (ERPs), as measured with EEG from the scalp surface). (Current research data do not allow us to satisfyingly answer the question of how particular physiological properties of single neurons and neural networks are differentially related to EEG oscillations in various frequency bands, for example gamma versus slow-frequency oscillations[80].) Analogously, it is conceivable that there will also be an impact on the variability of the BOLD brain response obtained with fMRI, as the BOLD response and LFPs covary substantially[99]. In other words, noisy spiking neurons should result in a variable (that is, noisier) electromagnetic field and BOLD response.

Both ERPs and the BOLD response thus make it possible to link predictions made from neural-network models with experimental neurophysiological and, by extension, behavioural data in humans. This creates a conceptual bridge between, on the one hand, molecular changes or pharmacological interventions that operate at the synaptic and single-neuron levels and, on the other hand, such large-scale and complex processes as memory and attention, for which global effects over thousands of neurons in the network are important. Following this line, computational network modelling can help to integrate experimental and clinical findings in neuropsychiatric disorders such as schizophrenia[38,68,72]. The prediction would be that normally higher firing rates increase the phase-locking of neuronal spiking activity or, more generally, the synchronous gain in the network[97] — this increase will be characterized by a more-regular interspike firing pattern[95], which should be accompanied by relatively little neurophysiological variability (noise) in EEG and fMRI measurements. Any factor that reduces the currents through the NMDARs on the pyramidal cells, as seems to occur in patients with schizophrenia[39], would decrease the firing rates of the set of activated neurons. These neurons would therefore fire more irregularly and be less synchronized — which should be reflected in a more variable (that is, noisier) BOLD and electromagnetic-field response — and thus would tend to make the network more distractible[6,38]. Overall, looking at the trial-by-trial variability of neural measures is currently the best way to relate experimental data to computational models (FIG. 3).

Signal-to-noise ratio in schizophrenia. During the past few years, increasing experimental evidence has indicated that the signal-to-noise ratio of brain activity is disturbed in individuals with schizophrenia. For example, EEG data revealed that information processing in patients with schizophrenia is characterized by a diminished cortical signal-to-noise ratio during tasks that require the allocation of attention and short-term memory (choice reaction time and oddball tasks)[17,18]. Specifically, they observed increased variability (noise) of event-related, stimulus-locked brain oscillations across a wide range of frequency bands (0.5–40 Hz) — so-called 'broadband noise' — in these tasks. In-depth analyses revealed that broadband noise resulted from a lack of phase locking of brain oscillations, and that diminished phase locking also predicted the amplitude of the averaged evoked response[17]; a similar observation was made for the gamma frequency band at ~40 Hz[100,101]. As the phase-response curve is a description of the relationship between the timing of each stimulus and the EEG response, these findings suggest that intrinsic cortical oscillators are impaired in schizophrenia. The abnormal phase locking that is observed across a wide range of frequencies in patients with schizophrenia (broadband phase synchrony) raises the possibility that there are intrinsic deficits in the brain circuitry that supports oscillations in several frequency bands (perhaps indicating increased noise in spiking neurons, as outlined above)[102–106]. It has been proposed[17] that this deficit might reflect specific changes of the attractor properties in cortical networks, most notably a decrease in attractor stability, which ultimately could account for the clinical symptoms of schizophrenia.

Since the initial report on increased broadband noise (as indicated by deficient broadband synchrony) in patients with schizophrenia[17], several independent electrophysiological and fMRI studies have confirmed and extended this finding[18,107–109] (FIG. 4). These studies also suggested that the increased noise in patients with schizophrenia is not limited to the gamma frequency band (~40 Hz) as first suggested by several groups[100,101], but that it is seen in various tasks, including short-term memory and attentional tasks, and in conjunction with steady-state visual responses that are used to test the frequency-response function of neural circuits. At the same time, these investigations showed that increased broadband noise is also present in healthy relatives of patients with schizophrenia who are considered to be at increased (genetic) risk for developing schizophrenia. These relatives were regarded as healthy because they did not show obvious signs of the positive symptoms that traditionally define the diagnosis of schizophrenia. However, rather poor cognitive performance was present in the relatives of patients with schizophrenia. It is therefore noteworthy that broadband noise was inversely correlated with cognitive performance — that is, attention and working memory — not only in patients with schizophrenia and their relatives but also in healthy control subjects[18]. Together, this work indicates that increased broadband noise could be considered a fundamental pathophysiological deficit in schizophrenia that can be related to the cognitive impairments of the illness and to genetic changes (see below). In addition, these studies provide an increasingly solid experimental basis on which to model this particular disturbance of brain function, which should allow researchers to generate new hypotheses on the molecular and physiological changes that underlie schizophrenia and the effects of drug treatment.

The role of prefrontal dopamine. What might cause the increased noise in the cortex of patients with schizophrenia? Here, we describe the evidence that abnormal dopamine modulation in the prefrontal cortex of patients with schizophrenia might influence the signal-to-noise ratio in this area and so contribute to the clinical symptoms of schizophrenia.

Event-related potentials
The potentials elicited in a brain area by the activity of neurons and their synaptic inputs in response to an event or stimulus.

Gamma frequency band
The spectral frequency band of the electrical activity of the brain that is close to 40 Hz.

Phase locking
Time locking of brain oscillations to (sensory) stimuli or (motor) responses.

Broadband phase synchrony
A measure of whether the energy in different spectral frequency bands of the electrical activity of the brain is in phase.

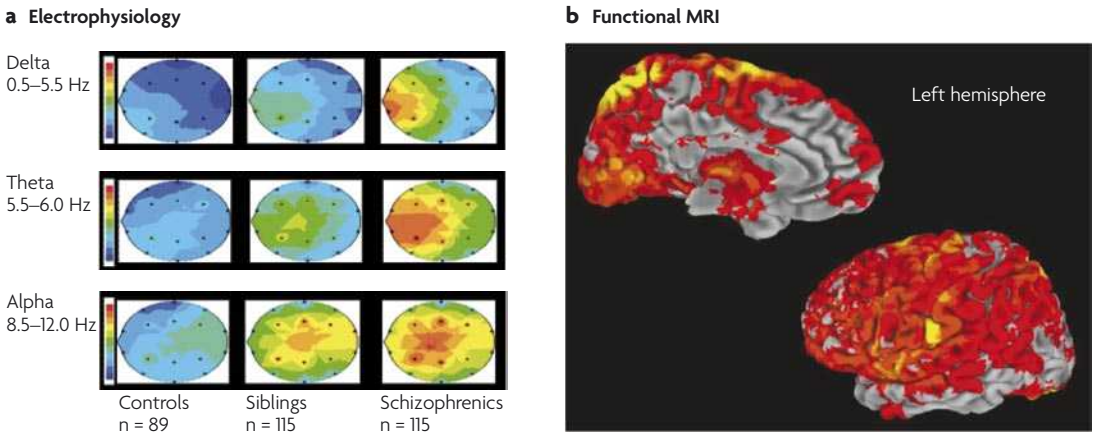


Figure 4 | **Increased cortical response variability ('noise') in patients with schizophrenia. a** | Frequency-domain analyses of event-related electroencephalogram (EEG) during an auditory oddball task, showing increased prefrontal noise — that is, increased variability of slow-wave oscillations — in patients with schizophrenia (right-hand column) and their clinically unaffected siblings (middle column) compared with control subjects (left-hand column)[18]. The variability of the slow-wave oscillations is depicted in different frequency bands: the delta band (top row), the theta band (middle row) and the alpha band (bottom row). Red indicates high EEG variability; blue indicates low EEG variability; yellow is intermediate. Increased variability of slow-wave oscillations results from impaired phase locking of these event-related oscillations in patients with schizophrenia[17]. Note that this study also provided evidence of increased 40 Hz gamma-band variability (noise) in patients with schizophrenia. **b** | An analogous increase in the variability (red colouring) of the blood-oxygen-level-dependent (BOLD) response is observed during a visual choice-reaction task in a contrast analysis of patients with schizophrenia (n = 12) and healthy control subjects (n = 16)[127]. Prefrontal noise is modulated by synaptic dopamine modulation (by the catechol-*O*-methyltransferase (*COMT*) genotype), as measured by electrophysiology and functional MRI[68,107,128]. Part **a** reproduced, with permission, from REF. 18 © (2004) American Psychiatric Association. Part **b** reproduced, with permission, from REF. 127 © (2006) American Psychiatric Association.

The hypothesis that dopamine might influence the signal-to-noise ratio was addressed in a study[110] that iontophoretically applied dopamine to the behaving macaque. The dopamine decreased the spontaneous firing rates of neurons in the putamen, the caudate nucleus and the adjacent prefrontal cortex. This type of dopamine effect could influence the neuronal signal (evoked response) to noise (spontaneous activity) ratio, and changes in the signal-to-noise ratio might therefore contribute to the behavioural disorders that result from dysfunctions of the dopamine system.

The idea that diminished prefrontal dopamine levels have a key role in the pathophysiology of schizophrenia, especially in the abnormal cognitive performance of patients with schizophrenia, is conceptually based on the work of Goldman-Rakic and colleagues, who extensively studied the effect of dopamine on prefrontal function in primates. This group used spatial working memory as a model system to show how dopamine in the prefrontal cortex is essential for frontal-lobe-related cognitive operations[111]. Further studies revealed that activation of D1 receptors can help to maintain neuronal activity in a delay task, whereas blockade of D1 receptors impairs it[112–114] and, in the prefrontal cortex, can produce short-term-memory deficits[115]. There is an inverted-U-shaped relationship between dopamine receptor activation and working-memory performance, in that excessive D1 receptor stimulation is as detrimental to cognitive performance as insufficient D1 receptor activation[116–118]. Under optimal neurochemical conditions, D1 receptor stimulation would decrease noise (in this case, neuronal responses to non-preferred spatial directions) and thereby improve the signal-to-noise ratio in the prefrontal cortex.

The role of D2 receptor stimulation or inhibition during cognitive operations in the prefrontal cortex seems to be complex, although the results of *in vitro* whole-cell patch-clamp recordings indicate that whereas D1 receptor activation increases NMDA and GABA conductances (a D1-receptor-dominated state), D2 receptor stimulation tends to have the opposite effect (a D2-receptor-dominated state)[65,86]. On the basis of these findings, several groups[9,65,67,119] predicted that D1 agonists and D2 antagonists should help to treat schizophrenic symptoms by increasing NMDAR- and GABAR-activated synaptic conductances. As indicated in FIG. 3b, the possible effect of D2 antagonists on the positive symptoms might be related to the increase in GABAR-activated currents[65,86], which would make the spontaneous firing state more stable. At the behavioural level, a D2 antagonist has been shown to impair set-shifting[120], which could be interpreted as a problem in shifting the activity from one attractor state to another, or as an overstability of the attractor system that controls which set is current. This could be caused by a shift of the activation ratio to the D1-receptor-dominated state, which causes a deepening of the attractor states (FIG. 2b). The phenomenon could be investigated in more detail in models of set-shifting, using the same attractor-based computational framework[121].

It was further hypothesized[68], on the basis of a post-mortem investigation[122], experimental evidence[123–125] and association studies of the catechol-*O*-methyltransferase (*COMT*) gene (for example, see REF. 126), that dopamine levels or signalling are reduced in the prefrontal cortex of patients with schizophrenia, and that decreased modulation by dopamine leads to reduced postsynaptic D1 receptor stimulation, changing the ratio of D1/D2 receptor activation in favour of D2 receptors (FIG. 5). Under this condition, a diminished D1/D2 receptor stimulation ratio would change a cascade of downstream molecular events and ultimately lead to impaired prefrontal neuronal-network stability that is associated with a decrease in the signal-to-noise ratio during information processing. A central part of this hypothesis was confirmed by an electrophysiological and fMRI study in humans[127,128]. Carriers of the Met allele of the COMT Val158Met polymorphism, who are thought to have higher prefrontal dopamine availability, showed lower frontal noise (and thus a stronger signal), suggesting that dopamine stabilizes cortical prefrontal microcircuits by increasing the signal-to-noise ratio (see also REF. 129).

Dopamine and signal-to-noise ratio. Durstewitz *et al.* addressed in a series of models[9,64] the effects of D1 receptor activation on the distractibility of networks. In these models, dopamine-dependent parameter shifts were applied to various variables in the network, such as AMPA, NMDA and GABA synaptic currents and the persistent Na^+ and inactivating K^+ membrane currents, and the network's distractibility was measured by determining what intensity of a distractor stimulus was needed to disturb an existing pattern in the network. The researchers found that increasing the dopamine effects on the network increased its robustness: D1 receptor activation made the network more resistant to distractors, owing to an increase in the energy barrier between different working-memory states[77]. This measure is directly related to robustness and distractibility, and serves as an important means by which to assess the modulation of the signal-to-noise ratio by the D1 receptor.

Brunel and Wang[7] simulated, in an integrate-and-fire attractor model of short-term memory, the effects of dopamine-induced changes on NMDAR-activated synaptic conductances. As described above, they introduced a model for D1 receptor activation in which this activation affects the NMDARs at excitatory pyramidal neurons and inhibitory interneurons to different degrees[130]. They incorporated the hypothesis that when the dopamine concentration increases, NMDA conductances on pyramidal cells increase earlier than those on interneurons. The result was an inverted-U-shaped relationship between synaptic activity and dopamine concentration, and this type of relationship has also been found in working-memory experiments[117]. Their analysis applied a mean-field technique, which reflects the mean firing rates of the neurons in a network without taking noise into account. As the signal is part of the signal-to-noise ratio, this can be seen as a first step to assessing the signal-to-noise ratio.

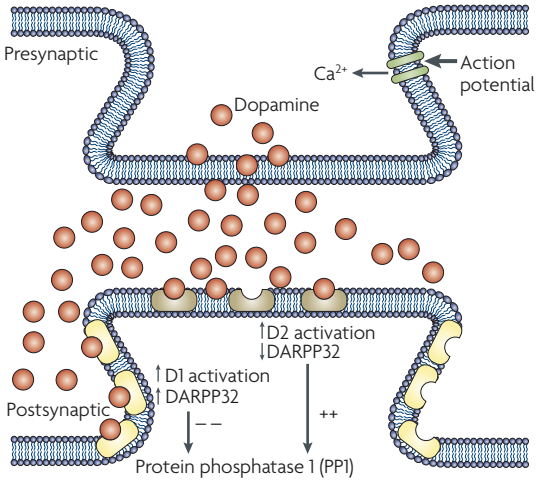


Figure 5 | **Molecular events following dopamine D1 and D2 receptor stimulation.** When synaptic dopamine concentrations are relatively high, dopamine will spillover out of the synaptic cleft (as depicted on the left half of the synapse), leading to extrasynaptic activation of D1 receptors (yellow) and, consequently, to a high D1/D2 activation ratio. Conversely, when synaptic concentrations are low (as depicted on the right half of the synapse), D2 receptors (brown) are predominantly activated, resulting in a low D1/D2 activation ratio. The relative input from both receptors is integrated by DARPP32 (dopamine- and cyclic AMP-regulated phosphoprotein of molecular weight 32 kDa), which determines the activity of protein phosphatase 1 (PP1). PP1 activity, in turn, affects ion-channel function by modulating the activity of NMDA (*N*-methyl-D-aspartate) receptors (that is, D1 stimulation increases and D2 stimulation decreases NMDA-mediated postsynaptic currents). This will ultimately have an impact on the signal-to-noise ratio. Figure reproduced, with permission, from REF. 131 © (2007) Georg Thieme Verlag.

To provide a theoretical framework for understanding the effects of synaptic currents on the signal-to-noise ratio in patients with schizophrenia, Loh, Rolls and Deco[38,73], using a similar network to that described above, directly analysed the signal-to-noise ratio that resulted from changes in the NMDA and GABA conductances, both of which are influenced by dopamine. Here, the trial-by-trial measure of stability, analogous to that which was used in the studies with humans[17,18,68,127,128], was defined as the ratio of trials on which the correct short-term memory state was maintained until the end of the trial (that is, the signal was present throughout) to trials on which the short-term memory state was no longer present at the end (that is, only noise remained). FIGURE 3a shows the signal-to-noise ratio that reflects this trial-by-trial variability. The performance differs between trials, even with the same set of parameters, because stochastic noise is generated by the random firing of the neurons (random firing varies between trials because a new seed for the random-number generator is used for each trial). We found that reducing the NMDA conductance, the GABA conductance or both decreased the signal-to-noise ratio,

Catechol-*O*-methyltransferase (*COMT*) gene
The gene that encodes the COMT enzyme, which provides one of the ways in which dopamine is degraded by methylation and therefore removed from the activity at a synapse. If *COMT* is too active there are likely to be low levels of dopamine in the prefrontal cortex, and this might be related to the cognitive symptoms of schizophrenia.

computed as the mean squared divided by the variance (FIG. 3a). (A similar measure has been used to determine the signal-to-noise ratio electrophysiologically from ERP scalp recordings in humans[17].)

Overall, these analyses suggest that reduced dopamine activity in patients with schizophrenia, by decreasing the NMDAR- and GABAR-activated synaptic currents, decreases the stability of short-term memory networks in the prefrontal cortex. This in turn increases the trial-by-trial variability: the memory states at the end of some of the trials would be incorrect owing to the decreased stability that results from the reduced depth of the basins of attraction and the stochastic-spike-firing-related noise in the network. The increased trial-by-trial variability could be measured as a decreased signal-to-noise ratio and impaired short-term-memory performance, and thus as reduced attention and performance on many of the cognitive tasks on which performance is impaired in patients with schizophrenia.

Conclusions and future directions

A reduction in the ion-channel currents that are activated by excitatory NMDARs and, to some extent, in the currents that are activated by inhibitory GABA receptors can diminish the stability — and thus increase the variability — of a neural network; this can be interpreted as a decrease in the signal-to-noise ratio[6,7,16,38,66,69,72,77]. This could account for some of the different symptoms of schizophrenia. Furthermore, alterations in the dopamine modulation of these processes might — partly by influencing the NMDAR-activated currents — contribute to the generation of these symptoms, including those symptoms that are thought to result from effects on the attractor networks in the prefrontal cortex that underlie short-term memory and attention. Specifically, diminished prefrontal D1 receptor efficacy, by reducing the signal-to-noise ratio of neural-network activity by lowering the NMDA currents, should reduce the stability of cortical neuronal networks[38,65,66,68,73,86,131].

In this Review we have focused on the role of dopamine as a classical neuromodulatory transmitter that, through its interaction with NMDARs, can have profound effects on postsynaptic responses and synaptic efficacy over a short timescale (~100 ms). In addition to these effects, the interaction between dopaminergic neurotransmission and NMDAR function can cause abnormal consolidation of short-term changes in synaptic efficacy into long-term changes, through long-term potentiation. Altered synaptic connection strength could lead to reduced connectivity, in accordance with the disconnection hypothesis of schizophrenia[59]. It will be interesting to consider, possibly in future computational studies, how these two accounts of dopamine — as a classical modulatory neurotransmitter and as an agent that can influence synaptic plasticity — could interact with each other.

The dynamical-systems framework, with its ability to investigate stability while taking into account neuronal spiking noise, provides a way to investigate how alterations in synaptic currents contribute to instability in attractor networks. In conjunction with experimental evidence, these models allow the generation of hypotheses regarding the neural basis of schizophrenic symptoms and how to treat them. We suggest that increasing both NMDAR- and GABAR-activated currents in the prefrontal and temporal cortices and synaptic prefrontal dopamine concentrations might help to reverse some of the symptoms of schizophrenia, and this has implications for current drug-development strategies for the disorder[132].

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Acknowledgements
This work was supported by the European Union, grant EC005-024; by the Spanish Research Project BFU2007-61710/BFI and CONSOLIDER INGENIO 2010 (G.D.); by two grants from the German Research Foundation (Deutsche Forschungsgemeinschaft): Wi1316/2-1 and Wi1316/2-2 (G.W.); by a Fellowship from the Fogarty Foundation (G.W.); by the Oxford McDonnell Centre for Cognitive Neuroscience (E.T.R.); and by the Boehringer Ingelheim Fonds (M.L.).

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Computational models of schizophrenia and dopamine modulation in the prefrontal cortex
Edmund T. Rolls, Marco Loh, Gustavo Deco, and Georg Winterer

For simulations of large attractor networks with noise, we used a mathematical formulation of the integrate-and-fire neurons and synaptic currents described in Brunel & Wang (2001). A detailed study of this system is published in Loh, Rolls & Deco (2007).

Simulation summary

We (Loh, Rolls & Deco 2007) assessed the stability of an integrate-and-fire simulation of a single attractor network with two possible short-term memory states stored in the increased excitatory synaptic strengths between two sets of neurons in the network. Both the ability of a short-term memory state to persist reliably, and the ability of the spontaneous firing state to remain stable and not enter one of the two attractors, were investigated. The spiking noise in the network was simulated, as the neurons in this model were spiking neurons.

When the attractor network was triggered into a high firing rate attractor state by stimulus S1 that was normally maintained until the end of a short term memory period, it was found that a reduction in the NMDA conductance reduced the stability of the high firing rate persistent attractor state, and frequently the state had been lost with only low, spontaneous, firing rates present at the end of a trial. In addition, the network was more distractible in that if a second stimulus S2 followed S1, the network was more likely to be distracted out of the S1 state. We hypothesized that such effects, if expressed in the dorsolateral prefrontal cortex, might be related to the cognitive symptoms, as they indicate reduced stability of the working memory. The reduction in NMDA conductances was shown to reduce the firing rates of the excitatory neurons, and this effect, when occurring in the orbitofrontal and anterior cingulate cortex, was related to the negative symptoms.

In the same simulations, a reduction in synaptic currents activated by GABA receptors produced a slight reduction in the stability of the spontaneous state (in that the network was more likely to jump to a high firing rate attractor state even if no stimulus had been presented), and an increased stability of the high firing rate persistent attractor state. When both NMDA and GABA are reduced one might think that these two counterbalancing effects (excitatory and inhibitory) would cancel each other out. However, this is not the case. The stability of both the spontaneous and the persistent states is reduced. Indeed, under these conditions, the network wandered freely between the two short-term memory states S1 and S2 in the network and the spontaneous state. We relate this pattern to the positive symptoms of schizophrenia, in which both the spontaneous and attractor states are shallow, and the system jumps, helped by the statistical fluctuations, between the different attractor states and the spontaneous state.

Neural and synaptic dynamics

The dynamics of the sub-threshold membrane potential V of neuron i are given by the equation:

$$C_{\mathrm{m}}\frac{dV(t)}{dt} = -g_{\mathrm{m}}(V(t) - V_L) - I_{\mathrm{syn}}(t), \quad (1)$$

Both excitatory and inhibitory neurons have a resting potential $V_L = -70$ mV, a firing threshold $V_{\rm thr} = -50$ mV and a reset potential $V_{\rm reset} = -55$ mV. The membrane parameters are different for both types of neurons: Excitatory (Inhibitory) neurons are modeled with a membrane capacitance $C_{\rm m} = 0.5$ nF (0.2 nF), a leak conductance $g_{\rm m} = 25$ nS (20 nS), a membrane time constant $\tau_{\rm m} = 20$ ms (10 ms), and a refractory period $t_{\rm ref} = 2$ ms (1 ms). Values are extracted from McCormick et al. (1985).

When the threshold membrane potential $V_{\rm thr}$ is reached, the neuron is set to the reset potential $V_{\rm reset}$ at which it is kept for a refractory period $t_{\rm ref}$ and the action potential is propagated to the other neurons.

The network is fully connected with $N_E = 400$ excitatory neurons and $N_I = 100$ inhibitory neurons, which is consistent with the observed proportions of the pyramidal neurons and interneurons in the cerebral cortex (Braitenberg & Schütz 1991, Abeles 1991). Full connectivity is a technical simplification, since cortical networks in the brain are usually sparsely connected. It enables faster simulations and, more importantly, the implementation of the mean-field approach. Nevertheless, the properties of attractor networks are still found with sparse connectivity (Treves & Rolls 1991). The synaptic current impinging on each neuron is given by the sum of recurrent excitatory currents ($I_{\rm AMPA,rec}$ and $I_{\rm NMDA,rec}$), the external excitatory current ($I_{\rm AMPA,ext}$), and the inhibitory current ($I_{\rm GABA}$):

$$I_{\rm syn}(t) = I_{\rm AMPA,ext}(t) + I_{\rm AMPA,rec}(t) + I_{\rm NMDA,rec}(t) + I_{\rm GABA}(t). \quad (2)$$

The recurrent excitation is mediated by the AMPA and NMDA receptors, and inhibition by GABA receptors. In addition, the neurons are exposed to external Poisson input spike trains mediated by AMPA receptors at a rate of 2.4 kHz. These can be viewed as originating from $N_{\rm ext} = 800$ external neurons at average rate of 3 Hz per neuron, consistent with the spontaneous activity observed in the cerebral cortex (Wilson et al. 1994, Rolls & Treves 1998). The currents are defined by:

$$I_{\rm AMPA,ext}(t) = g_{\rm AMPA,ext}(V(t) - V_E) \sum_{j=1}^{N_{\rm ext}} s_j^{\rm AMPA,ext}(t) \quad (3)$$

$$I_{\rm AMPA,rec}(t) = g_{\rm AMPA,rec}(V(t) - V_E) \sum_{j=1}^{N_E} w_{ij}^{\rm AMPA} s_j^{\rm AMPA,rec}(t) \quad (4)$$

$$I_{\rm NMDA,rec}(t) = \frac{g_{\rm NMDA}(V(t) - V_E)}{1 + [{\rm Mg}^{++}]\exp(-0.062V(t))/3.57} \times \sum_{j=1}^{N_E} w_{ij}^{\rm NMDA} s_j^{\rm NMDA}(t) \quad (5)$$

$$I_{\rm GABA}(t) = g_{\rm GABA}(V(t) - V_I) \sum_{j=1}^{N_I} w_{ij}^{\rm GABA} s_j^{\rm GABA}(t) \quad (6)$$

where $V_E = 0$ mV, $V_I = -70$ mV, w_{ij} is the synaptic weight from neuron j to neuron i, s_j refers to the fractions of open channels for the different receptors, and g refers to the synaptic conductances for the different channels. The NMDA synaptic current depends on the membrane potential and the extracellular concentration of Magnesium ($[{\rm Mg}^{++}] = 1$ mM, Jahr & Stevens (1990)). The values for the synaptic conductances for excitatory neurons are $g_{\rm AMPA,ext} = 2.08$ nS, $g_{\rm AMPA,rec} = 0.208$ nS, $g_{\rm NMDA} = 0.654$ nS and $g_{\rm GABA} = 2.50$ nS; and for inhibitory neurons $g_{\rm AMPA,ext} = 1.62$ nS, $g_{\rm AMPA,rec} = 0.162$ nS, $g_{\rm NMDA} = 0.516$

nS and $g_{\mathrm{GABA}} = 1.946$ nS. These values are obtained from the ones used by Brunel & Wang (2001) by correcting for the different numbers of neurons. The conductances were calculated so that in an unstructured network the excitatory neurons have a spontaneous spiking rate of 3 Hz and the inhibitory neurons a spontaneous rate of 9 Hz. The fractions of open channels are described by:

$$\frac{ds_j^{\mathrm{AMPA,ext}}(t)}{dt} = -\frac{s_j^{\mathrm{AMPA,ext}}(t)}{\tau_{\mathrm{AMPA}}} + \sum_k \delta(t - t_j^k) \quad (7)$$

$$\frac{ds_j^{\mathrm{AMPA,rec}}(t)}{dt} = -\frac{s_j^{\mathrm{AMPA,rec}}(t)}{\tau_{\mathrm{AMPA}}} + \sum_k \delta(t - t_j^k) \quad (8)$$

$$\frac{ds_j^{\mathrm{NMDA}}(t)}{dt} = -\frac{s_j^{\mathrm{NMDA}}(t)}{\tau_{\mathrm{NMDA,decay}}} + \alpha x_j(t)(1 - s_j^{\mathrm{NMDA}}(t)) \quad (9)$$

$$\frac{dx_j(t)}{dt} = -\frac{x_j(t)}{\tau_{\mathrm{NMDA,rise}}} + \sum_k \delta(t - t_j^k) \quad (10)$$

$$\frac{ds_j^{\mathrm{GABA}}(t)}{dt} = -\frac{s_j^{\mathrm{GABA}}(t)}{\tau_{\mathrm{GABA}}} + \sum_k \delta(t - t_j^k), \quad (11)$$

where $\tau_{\mathrm{NMDA,decay}} = 100$ ms is the decay time for NMDA synapses, $\tau_{\mathrm{AMPA}} = 2$ ms for AMPA synapses (Hestrin et al. 1990, Spruston et al. 1995) and $\tau_{\mathrm{GABA}} = 10$ ms for GABA synapses (Salin & Prince 1996, Xiang et al. 1998); $\tau_{\mathrm{NMDA,rise}} = 2$ ms is the rise time for NMDA synapses (the rise times for AMPA and GABA are neglected because they are typically very short) and $\alpha = 0.5$ ms^{-1}. The sums over k represent a sum over spikes formulated as δ-Peaks $\delta(t)$ emitted by presynaptic neuron j at time t_j^k.

The equations were integrated numerically using a second order Runge-Kutta method with step size 0.02 ms. The Mersenne Twister algorithm was used as random number generator for the external Poisson spike trains and different trials for equal parameter configurations were run with different random seeds (as the only difference).

Connection Matrices

For the simulations, we (Loh, Rolls & Deco 2007) used a simple system consisting of two selective pools (S1, S2), one non-selective pool (NS) and one inhibitory pool (IH). This is the minimal architecture to study stability and distractibility. The network structure between excitatory neurons was set up by Hebbian principles: Neurons within the same populations are more strongly connected than neurons in different populations. Neurons within each of the specific excitatory populations S1 and S2 are mutually coupled with a strong weight w_+. Since the populations S1 and S2 encoding different items have uncorrelated activity, these have a weaker connection strength w_- between them. Neurons in the inhibitory population are mutually connected with an intermediate weight $w = 1$. They are also connected with all excitatory neurons with the weight $w = 1$. Neurons in a specific excitatory population are connected to neurons in the nonselective population in the same layer with a feedforward synaptic weight $w = 1$ and a feedback synaptic connection of weight w_-.

Fraction of pool sizes f_i

Values are relative to all neurons, not only the excitatory portion.

S1	S2	NS	IH
0.08	0.08	0.64	0.2

Connection matrix for AMPA and NMDA – [from, to]

	S1	S2	NS	IH
S1	w_+	w_-	1	1
S2	w_-	w_+	1	1
NS	w_-	w_-	1	1
IH	0	0	0	0

where $w_- = \frac{0.8 - f_{S1} w_+}{0.8 - f_{S1}}$.

Connection matrix for GABA – [from, to]

	S1	S2	NS	IH
S1	0	0	0	0
S2	0	0	0	0
NS	0	0	0	0
IH	1	1	1	1

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