Neuroscience and Biobehavioral Reviews 35 (2011) 1644–1653

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Review

A computational neuroscience approach to schizophrenia and its onset

Edmund T. Rolls[a,*], Gustavo Deco[b,c]

[a] Oxford Centre for Computational Neuroscience, Oxford, UK
[b] Computational Neuroscience, Universitat Pompeu Fabra, Barcelona, Spain
[c] Institució Catalana de Recerca i Estudis Avançats, Barcelona, Spain

ARTICLE INFO

Article history:
Received 8 April 2010
Received in revised form 12 August 2010
Accepted 2 September 2010

Keywords:
Schizophrenia
Adolescence
Computational neuroscience
Synaptic pruning
Grey matter volume
NMDA receptors
Dopamine
GABA inhibition
Attractor networks
Neural networks
Stochastic neurodynamics
Noise in the brain
Neuronal spiking

ABSTRACT

Computational neuroscience integrate-and-fire attractor network models can be used to understand the factors that alter the stability of cortical networks in the face of noise caused for example by neuronal spiking times. A reduction of the firing rates of cortical neurons caused for example by reduced NMDA receptor function (present in schizophrenia) can lead to instability of the high firing rate attractor states that normally implement short-term memory and attention, contributing to the cognitive and negative symptoms of schizophrenia. Reduced cortical inhibition caused by a reduction of GABA neurotransmission (present in schizophrenia) can lead to instability of the spontaneous firing states of cortical networks, leading to a noise-induced jump to a high firing rate attractor state even in the absence of external inputs, contributing to the positive symptoms of schizophrenia. We consider how effects occurring at the time of late adolescence including synaptic pruning, decreases in grey matter volume, and changes in GABA-mediated inhibition and dopamine may contribute to the onset in some individuals of schizophrenia at this time.

Contents

* Corresponding author.
E-mail address: Edmund.Rolls@oxcns.org (E.T. Rolls).
URL: http://www.oxcns.org (E.T. Rolls).

0149-7634/$ – see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.neubiorev.2010.09.001

1. Introduction

In this paper, first we describe a computational neuroscience approach to schizophrenia. Then we consider how brain changes that occur in late adolescence may contribute to the onset of schizophrenia.

The computational neuroscience approach we take involves modeling cortical systems at the level of integrate-and-fire neurons with synaptically activated ion channels in attractor or autoassociation networks implemented with the recurrent collateral connections between pyramidal cells. This enables us to link from effects expressed at synapses and ion channels, through their effects on the spiking neuronal activity in the network and the noise that this introduces into the system, to global effects of the network such as the stability of short-term memory, attentional, and decision-making systems, and thus to cognitive function, dysfunction, and behavior. This provides a unifying approach to many aspects of cortical function, which helps in the understanding of short-term memory, long-term memory, top-down attention, decision-making, executive function, and the relation between the emotional and the reasoning systems in the brain (Deco and Rolls, 2003, 2005a, 2006; Deco et al., 2009; Rolls, 2008, 2010a,b; Rolls and Deco, 2002, 2010). This paper is the first in which we have linked this approach to how brain changes at the time of adolescence might influence some of these functions.

2. A top-down computational neuroscience approach to schizophrenia

Some computational neuroscience approaches to schizophrenia build upon single-neuron biophysics, physiology, and pharmacology in schizophrenia, and analyze their effects in neural networks, which are then linked to the symptoms of schizophrenia (Durstewitz et al., 1999, 2000; Durstewitz and Seamans, 2008; Seamans and Yang, 2004; Winterer and Weinberger, 2004).

We have adopted a *top-down* approach which considers whether generic alterations in the operation and stability of cortical circuits in different cortical areas might lead to the different symptoms of schizophrenia (Loh et al., 2007a,b; Rolls, 2005, 2008; Rolls et al., 2008b). Bottom-up approaches start with putative changes at the neural level such as alterations in dopamine, and try to understand the implications for function, which are of course multiple, of these changes. The top-down approach complements the bottom-up approaches, as it starts from the set of symptoms and maps them onto a dynamical systems computational framework. The dynamical systems computational approach considers factors that affect the stability of networks in the brain, and the effects of noise in those networks on the stability. Because the dynamical systems we consider can be, and are, implemented at the level of integrate-and-fire neurons with neuronal and synaptic dynamics that are biophysically realistic, and incorporate different classes of ion channel activated by different transmitter receptors, effects of changes at these different levels, including alterations in ion channels and transmitters, can be investigated in and predicted from the model. We call this class of model "mechanistic", in that it describes the underlying neuronal and subneuronal mechanisms involved in the dynamics in a biologically plausible way, so that predictions can be made about how changes in any one part of the mechanism will affect the overall, "global", operation of the system, measured for example by the stability of short-term memory and attentional states. Thus the top-down approach emphasizes how the computations in the system perform particular functions, and then considers how possibly combinations of several neural changes can influence the operation of the system, and how alterations of a number of possible different neural factors may be able to restore the computational functions being performed by the neural system.

We contrast this with phenomenological models, which attempt to capture the behavior of the system, but without regard to whether the system could be implemented in the brain, and without any neurally plausible mechanism being modelled. An example is the accumulator model of decision-making, in which an accumulator (linear adder) adds up each of the two (or more) inputs it receives, adds some noise, and then considers that a decision has been taken when some arbitrary threshold is reached in which the sum of one of the inputs is by some amount greater than the other (Ratcliff et al., 1999; Smith and Ratcliff, 2004; Vickers, 1979). Such a phenomenological model does not allow any direct predictions about how changes in ion channels, neurotransmitters, etc. alter the operation of the system, and indeed, to make such predictions, the phenomenological model, which may not represent realistically the type of processing that occurs in the brain, would itself have to be modelled in a neural system. Similar issues arise with connectionist models (Cohen and Servan-Schreiber, 1992) described elsewhere (Rolls et al., 2008b) which also do not incorporate details of the neurophysiological and biophysical mechanisms that contribute to the neural dynamics, and may therefore be less able to model how changes in a number of neurobiological factors influence the operation of the system. The mechanistic approach we adopt instead often is able to provide accounts for how important functional properties of the system arise as emergent properties of the system. One example is Weber's law in decision-making (Deco and Rolls, 2006). Another example is confidence in a decision that has been made, which is encoded in the firing rates of the neurons in the winning attractor (Rolls and Deco, 2010; Rolls et al., 2010a,b).

The stochastic dynamical systems approach that we utilize (Rolls and Deco, 2010) is introduced in Section 8. The full implementation of the equations for the neuron and synaptic dynamics is described elsewhere (Loh et al., 2007a; Rolls et al., 2008b), and includes currents passing through voltage-dependent and hence non-linear ion channels activated by NMDA receptors, and currents through ion channels activated by AMPA and GABA receptors. The positive feedback in the recurrent collateral connections in the network, the NMDA receptor non-linearity, and the non-linearity introduced by the threshold for firing of the neurons in the system, provide the system with non-linearities that enable it to have the properties of an attractor network (Deco and Rolls, 2005b; Rolls and Deco, 2010).

A feature that we have adopted from Brunel and Wang (2001) of the approach we use is a mean-field equivalent analysis of the network using techniques from theoretical physics. This allows measurement of the fixed points of the system, the flow in the system, and the operating areas in the parameter spaces that will produce for example a stable spontaneous firing rate and also stable high firing rates for each of the memory attractor states (depending on the starting conditions) in a noiseless system, equivalent to a system of infinite size (Brunel and Wang, 2001; Deco and Rolls, 2006; Loh et al., 2007a; Rolls and Deco, 2010). This enables suitable values of for example the synaptic connection weights in the system to be chosen. If these parameters are then used in the integrate-and-fire version of the model, which has noise due to the approximately Poisson spiking times of the neurons, the effects of the noise on the operation of the system, and of alterations for example of the different synaptic currents produced through different transmitter receptors in the system, can be investigated (Brunel and Wang, 2001; Deco and Rolls, 2006; Loh et al., 2007a; Rolls and Deco, 2010; Rolls et al., 2008a,b).

3. A neurodynamical hypothesis of schizophrenia

3.1. Cognitive symptoms

The cognitive symptoms of schizophrenia include distractibility, poor attention, and the dysexecutive syndrome (Green, 1996; Liddle, 1987; Mueser and McGurk, 2004). It has been suggested that at the core of the cognitive symptoms of schizophrenia is a working-memory deficit characterized by a difficulty in maintaining items in short-term memory implemented in the dorsolateral prefrontal cortex (Goldman-Rakic, 1994, 1999).

Short-term memory is implemented in the prefrontal cortex as follows. 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 (Abeles, 1991; Braitenberg and Schütz, 1991). These local recurrent collateral excitatory connections provide a positive-feedback mechanism (which is kept under control by GABA inhibitory interneurons) that enables a set of neurons to maintain their activity for many seconds to implement a short-term memory (Goldman-Rakic, 1995). Each memory is formed by the set of the neurons in the local cortical network that were coactive when the memory was formed, resulting in strengthened excitatory connections between that set of neurons through the process of long-term potentiation, which is a property of these recurrent collateral connections. 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, and so produces the completion of an incomplete memory. 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 subset of the neurons being active; any one subset of neurons can represent a short-term memory. The operation and properties of attractor networks are described in Section 8 and more fully elsewhere (Amit, 1989; Hertz et al., 1991; Hopfield, 1982; Rolls, 2008; Rolls and Deco, 2002, 2010).

Attractor networks appear to operate in the prefrontal cortex, an area that is important in attention and short-term memory, as shown for example by firing in the delay period of a short-term memory task (Funahashi et al., 1989; Fuster, 1995, 2000; Fuster and Alexander, 1971; Goldman-Rakic, 1996; Kubota and Niki, 1971; Rolls, 2008). Short-term memory is the ability to hold information on-line during a short time period (Fuster, 1995, 2000) and is fundamental to top-down attention in the sense that whatever requires attention (e.g. 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; the result is an advantage in the neuronal competition between the multiple inputs for the item that receives top-down bias from the short-term memory (Deco and Rolls, 2005a; Desimone and Duncan, 1995; Rolls and Deco, 2002). The impairments of attention induced by prefrontal cortex damage may be accounted for in large part by an impairment in the ability to hold the object of attention stably and without distraction in the short-term memory systems in the prefrontal cortex (Goldman-Rakic, 1996; Goldman-Rakic and Leung, 2002; Rolls, 2008).

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 (Frith and Dolan, 1997; Loh et al., 2007a; Seidman et al., 1994; Weinberger and Berman, 1996). Indeed, building on work by Seamans and Yang (2004), Rolls, Loh and Deco (Loh et al., 2007a; Rolls, 2005) have proposed that the working-memory and attentional deficits might be related to instabilities of the high-firing

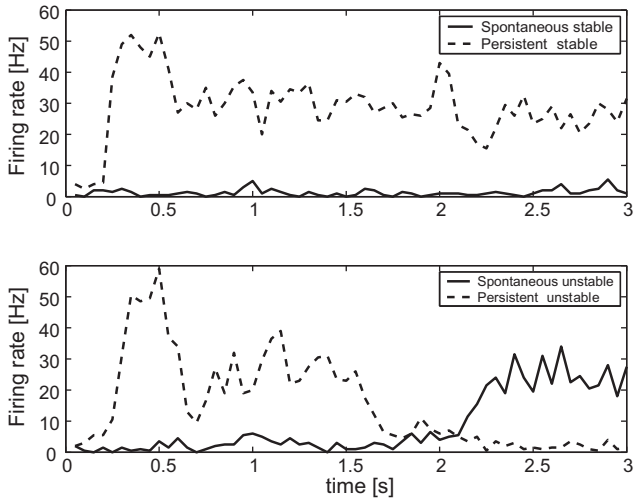

Fig. 1. Example trials of integrate-and-fire attractor network simulations of short-term memory. The average firing rate of all the neurons in the short-term memory population S1 of neurons is shown. (Top: normal operation) On a trial in which a recall stimulus was applied to S1 at 0–500 ms, firing continued normally until the end of the trial in the 'persistent' simulation condition. On a trial on which no recall stimulus was applied to S1, spontaneous firing (i.e. at a low rate) continued until the end of the trial in the 'spontaneous' simulation condition. (Bottom: unstable operation). On this persistent condition trial, the firing decreased during the trial as the network fell out of the attractor because of the statistical fluctuations caused by the spiking dynamics. This type of instability is more likely if NMDA receptor activated ion channel currents become decreased, or by other factors that decrease neuronal excitability. This provides a model of impaired cognitive function in for example schizophrenia. On the spontaneous condition trial, the firing increased during the trial because of the statistical fluctuations. This type of instability is more likely if GABA receptor activated ion channel currents become decreased, or by other factors that decrease cortical inhibition. This type of instability in which a network jumps because of noise into a high firing rate state that is not triggered by an external input to the network contributes it is suggested to the positive symptoms of schizophrenia. (After Rolls et al. (2008a).)

states in attractor networks in the prefrontal cortex (Fig. 1). Specifically, NMDA receptor hypofunction, which has been associated with schizophrenia (Coyle, 2006; Coyle et al., 2003), results in reduced currents running through NMDA receptor-activated ion channels; this causes neurons to fire less fast, leading to shallower basins of attraction (see Section 8) of the high firing-rate attractor states of the network (Loh et al., 2007a). The shallower basins of attraction arise firstly because with the neurons firing less fast, there is less positive feedback in the recurrent collateral connections between the neurons in the attractor, and this makes the system more vulnerable to noise. The noise could be external to the network, but an important source of noise that can destabilize the high firing rate attractor state is the random spiking times of neurons for a given mean firing rate, which produce statistical fluctuations by which there might due to a random set of events be less (or more) firing in a set of neurons than average, which could make the system fall out of a high firing rate attractor state (Rolls and Deco, 2010). (The spike times of individual neurons are close to being Poisson distributed.)

A second way in which reduced NMDA receptor function (or other factors such as synaptic pruning) could decrease the depth of the basins of attraction is by making the strengths of the synaptic connections between the neurons in the attractor weaker, which again reduces the positive feedback between the neurons in the attractor, and makes the attractor state more vulnerable to noise. These concepts are made quantitative in Section 8, Eq. (1), and in *The Noisy Brain* (Rolls and Deco, 2010). Thus, the stability of the attractor state is reduced. The result is difficulty in maintaining short-term memory and thus attention (see Fig. 1 and also Durstewitz, 2007; Durstewitz and Seamans, 2002). The shallower basins of attrac-

tion and the reduced time constant of the system caused by NMDA receptor (NMDAR) hypofunction (Wang, 2006), in the presence of the stochastic firing-related noise in the networks, result in distractibility, poor attention and working-memory difficulties.

3.2. Negative symptoms

The negative symptoms represent a complex of symptoms including apathy, poor rapport, lack of spontaneity, motor retardation, disturbance of volition, blunted affect, and emotional withdrawal and passive behavior (Liddle, 1987; Mueser and McGurk, 2004). The negative symptoms and cognitive deficits are highly correlated in patients with schizophrenia and their non-psychotic relatives (Bilder et al., 2002; Delawalla et al., 2006; Jacobs et al., 2007). Rolls, Loh and Deco propose that the negative symptoms are also related to the decreased firing rates caused by a reduction in currents through NMDAR-activated channels, but in brain regions that may include the orbitofrontal cortex and anterior cingulate cortex (Loh et al., 2007a; Rolls, 2005, 2008) rather than the prefrontal cortex. Indeed, lesions in these brain areas are well known to produce symptoms that resemble the negative symptoms in schizophrenia, and neuronal firing rates and BOLD activations in these regions are correlated with reward value and pleasure (Paus, 2001; Rolls, 1999, 2005, 2006, 2008; Rolls and Grabenhorst, 2008; Winterer et al., 2002).

This is a unifying approach to the cognitive and negative symptoms: the same reduction in NMDAR-activated channel currents produces on the 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 cortex, leading to the negative symptoms. In addition to the reduced emotion caused by the reduced firing rates, attractor networks may be present in the orbitofrontal cortex that help to maintain mood state (Rolls, 2008), and a decrease in their stability by the reduced depth in the basins of attraction could make emotions more labile in schizophrenia/schizoaffective disorder.

3.3. Positive symptoms

The positive symptoms of schizophrenia include bizarre trains of thoughts, hallucinations, and delusions (Liddle, 1987; Mueser and McGurk, 2004). In contrast to the cognitive and negative symptoms, the positive symptoms generally occur intermittently during the course of the illness, and this clinical state is called "psychosis". Rolls, Loh and Deco propose that owing to reduced currents through NMDAR-activated channels, the basins of attraction of the high-firing-rate attractor states are shallow (Durstewitz, 2007; Loh et al., 2007a; Rolls, 2005) 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 (see Figs. 1 and 2). Such thoughts might eventually be associated together in semantic memory, leading to false beliefs and delusions (Rolls, 2005, 2008).

In addition, Loh et al. (2007a) propose that a reduction in GABA interneuron efficacy in schizophrenic patients may 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. This is illustrated in Fig. 1 (bottom). On the spontaneous condition trial, the firing, which should have remained low throughout the trial as no cue was provided to start up the short-term memory, increased during the trial because of the statistical fluctuations, that is the spiking-related randomness in the network. This type of instability is more likely if GABA receptor activated ion channel currents become decreased, or by other factors that decrease cortical inhibition. This type of instability in which a network jumps because of noise into a high firing rate state that is not triggered by an external input to the network contributes it is suggested to the positive symptoms of schizophrenia, including for example hallucinations, delusions, and feelings of lack of control or being controlled by others (Loh et al., 2007a; Rolls et al., 2008b). Empirical evidence supports this computational proposal: markers indicating decreased inhibition by the GABA system are found in neocortical areas (Lewis et al., 2005) and in parts of the hippocampus (Benes, 2010). On the basis of this model, we have proposed (Loh et al., 2007a; Rolls et al., 2008b) that treating schizophrenia patients with D2 antagonists could increase the GABA currents (Seamans et al., 2001; Seamans and Yang, 2004) in the networks, which would alleviate the positive symptoms by reducing the spontaneous firing rates, which would deepen the spontaneous attractor state (see Figs. 1 and 3). This effect of D2 antagonists leaves the persistent attractors shallow because the high firing rates are reduced, which may explain why the D2 antagonists do not have a major effect on the negative and cognitive symptoms. To target negative symptoms, we have suggested that D1 agonists may help to deepen the basin of attraction of the high-firing-rate attractor state (Loh et al., 2007a; Rolls et al., 2008b). 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: modeling these conditions showed that the stability of both the spontaneous and the high-firing-rate states is reduced (Loh et al., 2007a) (see also Brunel and Wang, 2001; Durstewitz and Seamans, 2002). Indeed, under these conditions, the network wandered freely between the two short-term memory (high firing-rate) states

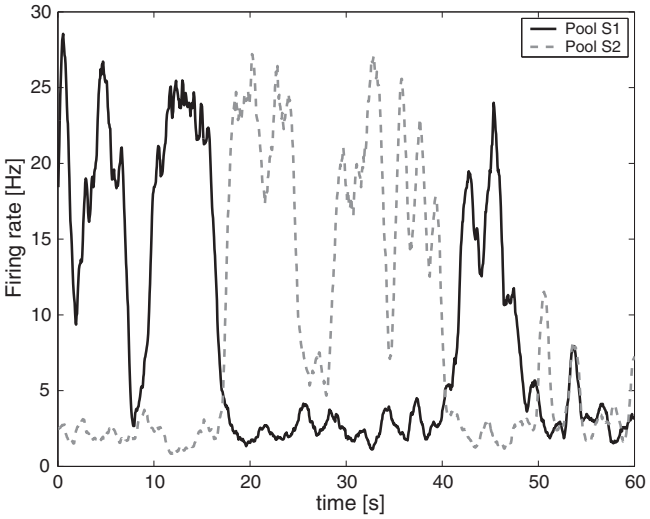

Fig. 2. Wandering between attractor states. An integrate-and-fire simulation of an attractor network with two memories stored in it, S1 and S2. With the normal synaptic efficacies, and no initial cue in the simulation, the network would stay stably in the spontaneous state with very little activity in the neurons in the S1 and S2 neuronal populations or pools. However, on trials of the type shown in which the NMDA conductances were reduced by 5% and GABA by 10%, the activity moves noisily between the attractor for the spontaneous state and the two persistent states S1 and S2 by virtue of statistical fluctuations 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 s sliding averaging window. (After Loh et al. (2007a).)

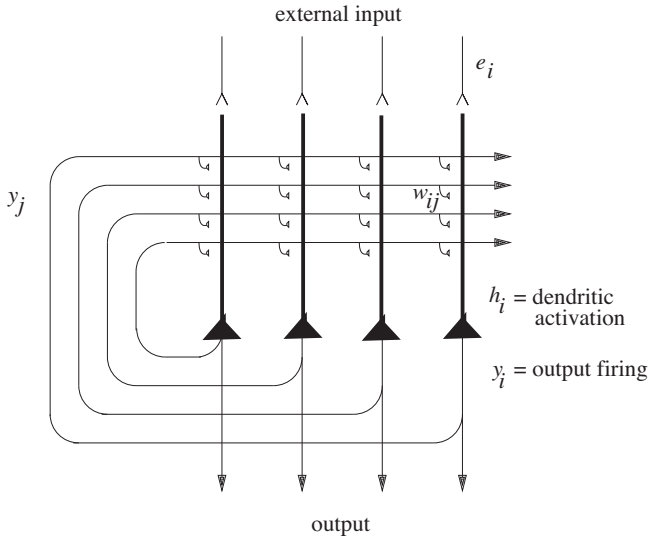

Fig. 3. The architecture of an autoassociation or attractor network (see Section 8.1).

in the network and the spontaneous state (Fig. 2). We relate this pattern to the positive symptoms of schizophrenia, in which both the basins of attraction of the spontaneous and high-firing-rate states are shallow, and the system jumps, helped by the statistical fluctuations, between the different attractor states and the spontaneous state (Fig. 2) (Loh et al., 2007a).

4. Schizophrenia and noise

The changes in the integrate-and fire model we have just described produced by alterations in the activation of synaptically activated ion channels can be interpreted in terms of a reduced signal-to-noise ratio. In the computational models, the 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 measured by the mean squared divided by the variance of the synaptic currents over the whole trial period (Loh et al., 2007a,b).

Three possible mechanisms for a decreased signal-to-noise ratio as reflected in reduced stability are highlighted by the computational models as follows, and may be relevant to the decreased signal-to-noise ratio described below in schizophrenia. First, reduced 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 face of spiking-related and other noise in the brain, and of distracting stimuli in the world. Second, the reduced contribution of NMDAR-activated current will reduce the time constant of the whole attractor network, also making the attractor states less stable in the face of noise and distracting stimuli. Third, reduced GABAR-mediated currents may 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 (Loh et al., 2007a,b).

A way to link the signal-to-noise ratio measure from models with experimental data is to use the trial-by-trial variability with experimental measures. With this approach, there is some evidence for decreased signal-to-noise ratio in schizophrenia, in studies in which the variability of EEG and functional neuroimaging data in attentional tasks is measured (Rolls et al., 2008b; Winterer et al., 2004, 2000).

5. The role of prefrontal cortex dopamine

With the computational approach described, links can be made to help understand the role of dopamine in schizophrenia (Rolls et al., 2008b). Dopamine, acting through D1 receptors, is important in maintaining high firing activity in prefrontal cortical networks involved in short-term memory and attention (Brozoski et al., 1979; Sawaguchi and Goldman-Rakic, 1991, 1994; Sawaguchi et al., 1988, 1990), with an optimal level being important (Goldman-Rakic et al., 2000; Vijayraghavan et al., 2007; Williams and Goldman-Rakic, 1995). Impairments in this system may contribute to the cognitive deficits in schizophrenia.

While D1 receptor activation increases NMDA and GABA receptor-activated ion channel conductances (a D1-receptor-dominated state), D2-receptor stimulation tends to have the opposite effect (a D2-receptor-dominated state) (Seamans et al., 2001; Seamans and Yang, 2004). On the basis of these findings, Seamans and Yang (2004) and others (Castner et al., 2000; Durstewitz, 2007; Durstewitz et al., 2000; Seamans and Yang, 2004) predict that D1 agonists and D2 antagonists should help to treat schizophrenic symptoms by increasing NMDAR- and GABA-R-activated synaptic conductances. Indeed, an important effect of D2 antagonists relates to the increase in GABA-R activated currents (Seamans et al., 2001; Seamans and Yang, 2004), which would make the spontaneous firing state more stable and may help to control the positive symptoms of schizophrenia (Rolls et al., 2008b).

6. Brain changes during adolescence that could influence these processes

There are marked changes in emotion, cognition, and behavior at the time of adolescence (Steinberg, 2005).

In relation to the cognitive symptoms of schizophrenia, there has always been the fact that schizophrenia is a condition that often has its onset in the late teens or twenties (Lewis and Levitt, 2002), and it has been suggested that there could be a link in this respect to changes in NMDA and related receptor functions that are related to aging (Rolls, 2008; Rolls and Deco, 2010). In particular, working memory shows a steady decline with age from the 20 s to the 70 s (Borella et al., 2008; Johnson et al., 2010; Swanson, 1999), and it may be the case that by the late teens or early twenties NMDA and related receptor systems (including dopamine) may be less efficacious than when younger, so that the cognitive symptoms of schizophrenia are more likely to occur at this age than earlier.

In this section, we examine some of the changes that occur in the brain during (late) adolescence, and address whether there is evidence that the changes that occur about this time, if interacting with other causal factors, could contribute to the onset of schizophrenia when it occurs in late adolescence and the early twenties. The computational points made next are clear, but the extent to which the changes in the brain lead them to apply is an area where further investigation is needed.

6.1. Grey matter and synaptic changes associated with adolescence

In the primate dorsolateral prefrontal cortex (DLPFC), the density of excitatory synapses decreases by 40–50% during adolescence, and this occurs without a major change in synaptic strength (Gonzalez-Burgos et al., 2008). Structural neuroimaging studies in humans demonstrate that adolescence is associated with a substantial decrease in cortical grey matter thickness (Giedd et al., 1999; Gogtay and Thompson, 2010), a decrease usually interpreted to result from the massive and increased synaptic pruning occurring during adolescence and early adulthood (Gogtay et al., 2004; Rakic,

1996; Rakic et al., 1994). Indeed, the total volume of grey matter increases across the cortex prior to puberty, reaching a peak somewhere in the early to-mid pubertal period after which there is a post-pubertal decline.

It is noted that a decreased density of dendritic spines (a marker of excitatory synaptic inputs to pyramidal neurons) in the DLPFC of individuals with schizophrenia (Garey et al., 1998; Glantz and Lewis, 2000), is consistent with reduced excitatory drive in DLPFC circuits in schizophrenia. In addition, convergent lines of evidence indicate that schizophrenia might be associated with reduced excitatory synaptic neurotransmission through NMDA (N-methyl-D-aspartate) glutamate receptors (Coyle, 2006; Coyle et al., 2003). Further, the loss of excitatory synapses is even greater at adolescence in those diagnosed with schizophrenia, amounting to 60% (Bennett, 2009; Glantz et al., 2007; Glantz and Lewis, 2000).

What are the functional and computational implications of this synaptic pruning and decrease in grey matter volume at the time of adolescence? A first possible computational implication is that neurons in the prefrontal cortex become less excitable, as they have fewer excitatory synapses. A decrease in the firing rates of these neurons could decrease the stability of cortical attractor networks that implement short-term memory, and attention. This could result, if added to other effects, in a tendency of some individuals at about the time of adolescence to show the cognitive changes of schizophrenia. Similarly, if the same pruning of excitatory synapses occurred in the orbitofrontal cortex and the firing rates of the neurons were lower as a result, this could result (in otherwise predisposed individuals) in some of the negative symptoms of schizophrenia (decreased emotionality and motivation) appearing at about this time. Whether changes in GABA compensate for the decreased excitatory drive to cortical pyramidal cells in adolescence is considered in Section 6.2. The argument here is that the massive and increased synaptic pruning in late adolescence/the early twenties (Gogtay et al., 2004; Rakic, 1996; Rakic et al., 1994) may be sufficiently large to reduce the stability of attractor networks involved in working memory, especially with the larger reduction in excitatory synapses found in schizophrenics (Bennett, 2009; Glantz et al., 2007; Glantz and Lewis, 2000). (Although synaptic pruning starts earlier in development, we do not know whether the synapses being pruned before and during early adolescence are computationally efficacious in these attractor networks (i.e. are on the right neurons to support attractors, and with the associatively increased synaptic strength required to support discrete attractor states (Rolls, 2008); and the synaptic pruning rate does become larger in late adolescence and the early twenties (Gogtay et al., 2004; Rakic, 1996; Rakic et al., 1994).)

A second computational implication of a reduced number of excitatory connections onto each neuron arises from the fact that the number of different memories that can be stored in an associative network is proportional to the number of associatively modifiable excitatory connections onto each neuron (Rolls, 2008; Rolls and Treves, 1998). This applies to both pattern association networks used to associate one stimulus with another, for example a visual stimulus with the sight of food (Rolls and Treves, 1990); and to autoassociation or attractor networks used to store a memory as a set of events, and later recall the whole memory from any part (Treves and Rolls, 1991). The number of different memories that can be stored in both types of associative network is of the order of the number of associatively modifiable connections onto each neuron if sparse representations are used (Rolls and Treves, 1990; Treves and Rolls, 1991). This number will be in the order of 10,000 for a network in a small, local, region of the neocortex (Rolls, 2008). The implication of a reduction in the number of associatively modifiable synapses onto each neuron will thus be a reduced memory capacity, and, particularly important in the present context, more interference between different memories (Rolls, 2008). This increased interference will tend to impair the distinctiveness and stability of any one memory by altering the shape of the energy landscape, and making the system more sensitive to the effects of noise generated by the Poisson nature of the spiking of neurons (Rolls, 2008; Rolls and Deco, 2010). This will for example tend to impair short-term memory and attention, and increase distractibility. A reduced number of synapses onto each neuron could, by the time of late adolescence, be sufficient to have therefore an impact on for example working memory, and this in individuals predisposed to schizophrenia could contribute to an account of why the cognitive symptoms of schizophrenia may become apparent in late adolescence or the early twenties.

6.2. GABA changes at adolescence

Any change during adolescence in the excitatory input to cortical pyramidal cells could be compensated by changes in the GABA inhibitory interneurons that receive from the pyramidal cells and provide negative feedback to them. No significant changes in the density of inhibitory synapses are observed in the neocortex during adolescence (De Felipe et al., 1997; Rakic et al., 1986). However, the efficacy of GABAergic transmission may change during adolescence because during this developmental period substantial changes occur in the levels of expression of $GABA_A$ receptors, GABA transporters, and parvalbumin, an interneuron-specific calcium binding protein (Lewis et al., 2004). Whether or not GABA-mediated transmission can regulate excitatory synaptic pruning during adolescence remains to be investigated.

In schizophrenia, a deficiency in signalling through the TrkB neurotrophin receptor leads to reduced GABA (gamma-aminobutyric acid) synthesis in the parvalbumin-containing subpopulation of inhibitory GABA neurons in the dorsolateral prefrontal cortex of individuals with schizophrenia. Despite both pre- and post-synaptic compensatory responses, there is a resulting decrease in the perisomatic inhibition of pyramidal neurons (Lewis et al., 2005). Moreover, markers indicating decreased inhibition by the GABA system were found in other neocortical areas (Lewis et al., 2005) and in parts of the hippocampus (Benes, 2010), of individuals with schizophrenia. As described in Section 3.3, a decrease in inhibition could decrease the stability of the spontaneous firing state of cortical attractor networks, and might least to spurious high firing rate states, which could contribute to the *positive* symptoms of schizophrenia.

6.3. Dopamine changes at adolescence

In primates, cortical and subcortical tissue concentrations of dopamine (DA) are increased during adolescence compared to childhood and adulthood (Goldman-Rakic and Brown, 1982; Irwin et al., 1994). In addition, DA innervation of the frontal cortex peaks during adolescence relative to childhood and adulthood, specifically in cortical layer III, which contains pyramidal cells responsible for cortico-cortical information processing (Rosenberg and Lewis, 1995). D1 and D2 receptor densities appear to decrease from adolescence to adulthood in both nonhuman primate and human cortex and subcortical regions, though peaks in receptor density occur in childhood (Jucaite et al., 2010; Lidow and Rakic, 1992; Seeman et al., 1987). Thus, cortical and subcortical regions undergo specific increases in DA concentrations and innervation during adolescence, with receptor levels decreasing from peaks achieved during childhood (Wahlstrom et al., 2010). It has been noted elsewhere that the ratio of D1 to D2 receptor mediated effects may be a relevant factor, with D1 receptor activation increasing NMDA and GABA conductances, and D2-receptor stimulation tending to have the opposite effect (Rolls et al., 2008b; Seamans et al., 2001; Seamans and Yang, 2004).

It has been suggested that increases in risk-taking and emotional lability at the time of adolescence could be related to heightened DA efficacy (Wahlstrom et al., 2010). According to this approach, DA underlies a behavioral activation system that modulates incentive-motivated approach behavior (Depue and Collins, 1999). This system promotes reward-seeking through activity in limbic, striatal, and frontal networks. It is suggested that the increase occurs via a tonic increase in DA availability which impacts both subcortical (limbic and striatal) and cortical (prefrontal) circuits, and produces over-activation of incentive motivation (Wahlstrom et al., 2010).

If there are impairments in the DA system that contribute to the cognitive deficits in schizophrenia (Goldman-Rakic, 1999; Rolls et al., 2008b), then it is possible that the decrease in D1 receptor binding from adolescence to adulthood in normal subjects (Jucaite et al., 2010) may have the effect of reducing the stability of cortical attractors (by reducing the firing rate of the neurons in part by reducing NMDA receptor mediated synaptic conductances) involved in cognitive functions in the prefrontal cortex such as short-term memory and attention. This decrease could be a factor that contributes to cognitive symptoms of schizophrenia tending to appear in late adolescence or early adulthood, by contributing to the instability of a system at that time that may already be less stable in those predisposed to have schizophrenia. Decreased affect, which could be related to decreased effects of rewards and punishers in the orbitofrontal cortex and related systems (Rolls, 2005), which may be modulated by dopamine, may appear at about the same time, if D1 receptors become reduced.

As noted in Sections 3.3 and 6.2, the use of D2 blockers in schizophrenia may not relate to these cognitive and emotional systems, but instead to increasing the activity of GABA systems which may help to control the positive symptoms (Rolls et al., 2008b).

7. Conclusions

We have reviewed a stochastic neurodynamics approach to schizophrenia, which suggests that:

A reduced depth in the basins of attraction of cortical attractor states destabilizes the activity at the network level due to the statistical fluctuations caused by the stochastic spiking of neurons.

A decrease in the NMDA receptor conductances, present in schizophrenia, which reduces the depth of the attractor basins, decreases the stability of short-term memory states and increases distractibility. The effects produced decrease the signal-to-noise ratio of the networks.

The cognitive symptoms of schizophrenia such as distractibility, working memory deficits or poor attention could be caused by this instability of attractor states in prefrontal cortical networks.

A reduction of dopamine in the prefrontal cortex, producing reduced dopamine D1 receptor activation in schizophrenia, acting at least in part by reducing NMDA receptor-activated synaptic currents, can produce similar effects.

A reduction of NMDA receptor-activated synaptic conductances, present in schizophrenia, produces lower firing rates in neurons, and in the orbitofrontal and anterior cingulate cortex could account for the negative symptoms including a reduction of emotions.

Decreasing the GABA as well as the NMDA conductances produces not only switches between the attractor states, but also jumps from spontaneous activity into one of the attractors. The spontaneous state of firing is less stable when GABA efficacy is reduced because there is less inhibition. 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. The instability that accounts for the positive symptoms we argue is due to less stability of the spontaneous (unstimulated) state of firing due to reduced GABA inhibition which leads to entry into a high firing state in the absence of a relevant stimulus; and is due also to less stability of the high firing rate states due to reduced NMDA receptor mediated neuronal activation so that a high firing rate state moves too freely into other high firing rate attractor states, or back to the spontaneous firing state.

This approach shows how any factors that reduce cortical excitability and any factors that reduce cortical inhibition can be interpreted in terms of the stochastic neurodynamics of cortical systems. This opens a way to interpret effects, possibly not yet discovered, that reduce cortical excitation, and/or reduce cortical inhibition, on the stability of cortical networks involved in cognitive functions. This approach also opens up new ways to explore combinations of treatments that by influencing these two sources of instability in cortical networks, altered excitation and altered inhibition, might ameliorate the instabilities, and improve functioning.

The approach described thus enables links to be made from factors that modulate currents in synapses, or the excitability of cortical neurons, or alterations in cortical inhibition, to the effects that these will have on the global function performed by a network, to implement for example cognitive processes such as short-term memory and attention.

In terms of some of the brain changes that are prominent at the time of adolescence, the following points can be made.

First, and this includes changes yet to be discovered or fully understood, one way in which the changes can be interpreted is in terms of their effects on the stochastic neurodynamics of the cerebral cortex. As we have seen, factors that decrease cortical excitability may produce cognitive changes such as alterations of short-term memory, attention, or executive function because of instability of the high firing rate attractor states. Further, factors that decrease cortical inhibition may produce cognitive changes because of instability of the low firing rate attractor states, which might be provoked by noise caused for example by the stochastic neuronal firing to lead to spurious states not produced by external inputs or requirements.

Second, in relation to the evidence that the synaptic pruning, and the reduction in grey matter volume, that normally take place during adolescence are especially marked in those who develop schizophrenia, this could lead to reduced cortical excitability, which would lead to cognitive and negative symptoms. This may provide an understanding of why schizophrenia has a tendency to become evident in late adolescence or the early twenties, as this is a time when cortical pruning is taking place especially rapidly, and even more rapidly in those diagnosed with schizophrenia.

Third, in so far as reduced NMDAR function is related to schizophrenia (Coyle, 2006), we might predict that this reduction would become especially evident in late adolescence especially in those who develop schizophrenia.

Fourth, given that the efficacy of GABAergic transmission may decrease during adolescence because of changes in the levels of expression of $GABA_A$ receptors, GABA transporters, and parvalbumin (an interneuron-specific calcium binding protein) (Lewis et al., 2004), and that reduced GABAergic inhibition of pyramidal neurons is associated with schizophrenia (Lewis et al., 2005), we might expect the stability of the spontaneous firing states to be reduced, and the positive symptoms to become evident at about this time.

Fifth, given that dopamine levels are high in adolescence compared to adulthood (Section 6.3), and that reduced dopamine partly by reducing NMDA currents may decrease cortical excitability and contribute to the cognitive and negative symptoms of schizophre-

nia (Section 3), it would be interesting to investigate whether dopamine levels or efficacy in those who become schizophrenic are low relative to the average especially at the time of adolescence.

8. Stochastic neurodynamics: appendix

8.1. The attractor framework

The attractor framework is important in many aspects of neural dynamics, including the systems that implement short-term memory, long-term memory, attention, and decision-making (Rolls, 2008; Rolls and Deco, 2002). In an attractor network of interconnected neurons, a memory pattern (or set of active neurons) can be stored by synaptic modification and activated by external inputs. When a retrieval cue is applied, the system moves towards one of the stored patterns, thus implementing memory retrieval. The system can implement memory retrieval in this way from an incomplete retrieval cue, implementing "completion". The retrieved pattern can be stably maintained by the system even after the input ceases (Hertz et al., 1991; Hopfield, 1982; Rolls, 2008). These patterns could correspond to memories, perceptual representations or thoughts. If several input cues are presented simultaneously, the non-linear dynamics results in one of the attractor states winning, and this implements a realistic model of decision-making in the brain (Deco and Rolls, 2006; Rolls and Deco, 2010; Wang, 2002, 2008). In all these dynamical processes, noise, in part due to the random spiking times of individual neurons (for a given mean rate), can make the processes in a finite-sized system stochastic, making the stability of the system, memory retrieval, and decision-making probabilistic, which, as we have shown elsewhere, can be advantageous (Rolls and Deco, 2010).

The architecture of an attractor or autoassociation network is as follows (see Fig. 3): external inputs e_i activate the neurons in the network, and produce firing y_i, where i refers to the i'th neuron. The neurons are connected by recurrent collateral synapses w_{ij}, where j refers to the j'th synapse on a neuron. By these synapses an input pattern on e_i is associated with itself, and thus the network is referred to as an autoassociation network. Because there is positive feedback via the recurrent collateral connections, the network can sustain persistent firing. These synaptic connections are assumed to build up by an associative (Hebbian) learning mechanism (Hebb, 1949; Rolls, 2008) (according to which the more two neurons are simultaneously active the stronger the neural connection becomes). The inhibitory interneurons are not shown. They receive inputs from the pyramidal cells, and make negative feedback connections onto the pyramidal cells 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 (Hopfield, 1982), where the energy would be defined as

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

where y_i is the firing of neuron i, and <y> indicates the average firing rate. The intuition here is that if both y_i and y_j are above their average rates, and are exciting 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.

Autoassociation attractor systems have two types of stable fixed point: 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 stimulus, 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.

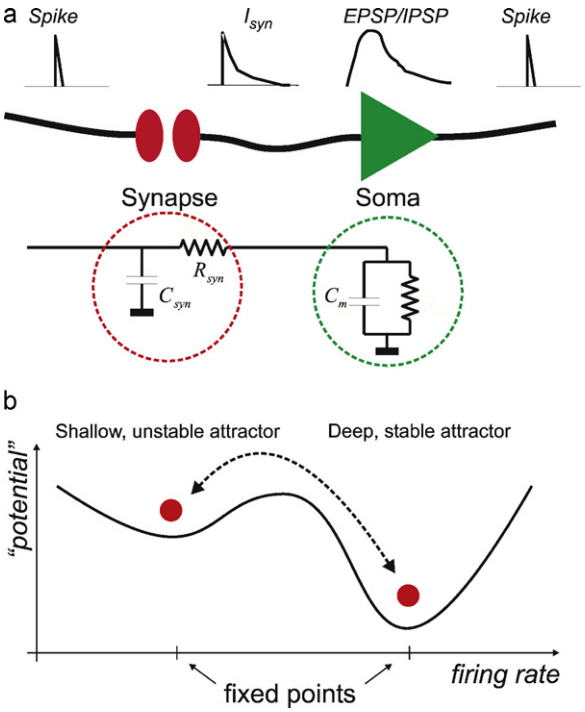

Fig. 4. (a) The neuronal components of an integrate-and-fire attractor network simulation (see Section 8.2). (b) The energy landscape of an integrate-and-fire attractor network simulation (see Section 8.2).

8.2. Energy landscape and stochasticity

Realistic attractor network architectures of the cerebral cortex are typically implemented by integrate-and-fire neurons and realistic synaptic dynamics (see Fig. 4a; Brunel and Wang, 2001; Deco and Rolls, 2006; Rolls and Deco, 2010). The integrate-and-fire model describes the subthreshold membrane potential, which is influenced by synaptic currents:

$$C_m \frac{dV(t)}{dt} = -g_m(V(t) - V_L) - I_{syn}(t)$$

$$I_{syn}(t) = g_s(V(t) - V_E)\sum_{j=1}^{N} w_{ij} s_j(t)$$

$$\frac{ds_j(t)}{dt} = -\frac{ds_j(t)}{\tau} + \sum_k \delta(t - t_j^k)$$

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 with time constant τ and 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} at which it is kept for a refractory period t_{ref} and the action potential is propagated to the other neurons. These networks can maintain a stable pattern of firing of a subset of neurons, which are strongly interconnected.

The attractor dynamics can be pictured by effective energy landscapes, which indicate the basin of attraction by valleys, and the attractor states or fixed points by the bottom of the valleys (see Fig. 4b). The stability of an attractor is characterized by the aver-

age 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 (i.e. the times at which each spike of a neurons occurs is random) and the finite-size effect due to the limited numbers of neurons in the network. In fact, the number of spikes emitted in a time interval dt by the network is a Poisson variable with mean and variance $Nr(t)\,dt$, where N is the number of neurons in the network and $r(t)$ the averaged firing rate at time t. The estimate of $r(t)$, is then a stochastic process $r_N(t)$, well described in the limit of large Nr 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 the depths of the attractors are shallow (as in the left compared to the right valley in Fig. 4b), less force is needed to move a ball from the shallow 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 (Rolls, 2008; Rolls and Deco, 2010).

Acknowledgments

This work was supported by the Oxford McDonnell Centre for Cognitive Neuroscience, and by the Oxford Centre for Computational Neuroscience. We acknowledge contributions by a number of colleagues to some of the work described, and the citations are provided.

References

Abeles, M., 1991. Corticonics—Neural Circuits of the Cerebral Cortex. Cambridge University Press, New York.
Amit, D.J., 1989. Modeling Brain Function. Cambridge University Press, Cambridge.
Benes, F.M., 2010. Amygdalocortical circuitry in schizophrenia: from circuits to molecules. Neuropsychopharmacology 35, 239–257.
Bennett, M.R., 2009. Synapse formation and regression in the cortex during adolescence and in schizophrenia. The Medical Journal of Australia 190, S14–S16.
Bilder, R.M., Goldman, R.S., Volavka, J., Czobor, P., Hoptman, M., Sheitman, B., Lindenmayer, J.P., Citrome, L., McEvoy, J., Kunz, M., Chakos, M., Cooper, T.B., Horowitz, T.L., Lieberman, J.A., 2002. Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. The American Journal of Psychiatry 159, 1018–1028.
Borella, E., Carretti, B., De Beni, R., 2008. Working memory and inhibition across the adult life-span. Acta Psychologica 128, 33–44.
Braitenberg, V., Schütz, A., 1991. Anatomy of the Cortex. Springer-Verlag, Berlin.
Brozoski, T.J., Brown, R.M., Rosvold, H.E., Goldman, P.S., 1979. Cognitive deficit caused by regional depletion of dopamine in prefrontal cortex of rhesus monkey. Science 205, 929–932.
Brunel, N., Wang, X.J., 2001. Effects of neuromodulation in a cortical network model of object working memory dominated by recurrent inhibition. Journal of Computational Neuroscience 11, 63–85.
Castner, S.A., Williams, G.V., Goldman-Rakic, P.S., 2000. Reversal of antipsychotic-induced working memory deficits by short-term dopamine D1 receptor stimulation. Science 287, 2020–2022.
Cohen, J.D., Servan-Schreiber, D., 1992. Context, cortex, and dopamine: a connectionist approach to behavior and biology in schizophrenia. Psychological Review 99, 45–77.
Coyle, J.T., 2006. Glutamate and schizophrenia: beyond the dopamine hypothesis. Cellular and Molecular Neurobiology 26, 365–384.
Coyle, J.T., Tsai, G., Goff, D., 2003. Converging evidence of NMDA receptor hypofunction in the pathophysiology of schizophrenia. Annals of the New York Academy of Sciences 1003, 318–327.
De Felipe, J., Marco, P., Fairen, A., Jones, E.G., 1997. Inhibitory synaptogenesis in mouse somatosensory cortex. Cerebral Cortex 7, 619–634.
Deco, G., Rolls, E.T., 2003. Attention and working memory: a dynamical model of neuronal activity in the prefrontal cortex. European Journal of Neuroscience 18, 2374–2390.
Deco, G., Rolls, E.T., 2005a. Attention, short-term memory, and action selection: a unifying theory. Progress in Neurobiology 76, 236–256.
Deco, G., Rolls, E.T., 2005b. Neurodynamics of biased competition and co-operation for attention: a model with spiking neurons. Journal of Neurophysiology 94, 295–313.
Deco, G., Rolls, E.T., 2006. Decision-making and Weber's Law: a neurophysiological model. European Journal of Neuroscience 24, 901–916.
Deco, G., Rolls, E.T., Romo, R., 2009. Stochastic dynamics as a principle of brain function. Progress in Neurobiology 88, 1–16.
Delawalla, Z., Barch, D.M., Fisher Eastep, J.L., Thomason, E.S., Hanewinkel, M.J., Thompson, P.A., Csernansky, J.G., 2006. Factors mediating cognitive deficits and psychopathology among siblings of individuals with schizophrenia. Schizophrenia Bulletin 32, 525–537.
Depue, R.A., Collins, P.F., 1999. Neurobiology of the structure of personality: dopamine, facilitation of incentive motivation, and extraversion. The Behavioral and Brain Sciences 22, 491–517, discussion 518–569.
Desimone, R., Duncan, J., 1995. Neural mechanisms of selective visual attention. Annual Review of Neuroscience 18, 193–222.
Durstewitz, D., 2007. Dopaminergic modulation of prefrontal cortex network dynamics. In: Tseng, K.-Y., Atzori, M. (Eds.), Monoaminergic Modulation of Cortical Excitability. Springer, New York, pp. 217–234.
Durstewitz, D., Kelc, M., Gunturkun, O., 1999. A neurocomputational theory of the dopaminergic modulation of working memory functions. Journal of Neuroscience 19, 2807–2822.
Durstewitz, D., Seamans, J.K., 2002. The computational role of dopamine D1 receptors in working memory. Neural Networks 15, 561–572.
Durstewitz, D., Seamans, J.K., 2008. The dual-state theory of prefrontal cortex dopamine function with relevance to COMT genotypes and schizophrenia. Biological Psychiatry 64, 739–749.
Durstewitz, D., Seamans, J.K., Sejnowski, T.J., 2000. Dopamine-mediated stabilization of delay-period activity in a network model of prefrontal cortex. Journal of Neurophysiology 83, 1733–1750.
Frith, C., Dolan, R.J., 1997. Brain mechanisms associated with top-down processes in perception. Philosophical Transactions of the Royal Society of London 352, 1221–1230.
Funahashi, S., Bruce, C.J., Goldman-Rakic, P.S., 1989. Mnemonic coding of visual space in monkey dorsolateral prefrontal cortex. Journal of Neurophysiology 61, 331–349.
Fuster, J.M., 1995. Memory in the Cerebral Cortex. MIT Press, Cambridge, MA.
Fuster, J.M., 2000. Executive frontal functions. Experimental brain research. Experimentelle Hirnforschung 133, 66–70.
Fuster, J.M., Alexander, G.E., 1971. Neuron activity related to short-term memory. Science 173, 652–654.
Garey, L.J., Ong, W.Y., Patel, T.S., Kanani, M., Davis, A., Mortimer, A.M., Barnes, T.R., Hirsch, S.R., 1998. Reduced dendritic spine density on cerebral cortical pyramidal neurons in schizophrenia. Journal of Neurology, Neurosurgery, and Psychiatry 65, 446–453.
Giedd, J.N., Blumenthal, J., Jeffries, N.O., Castellanos, F.X., Liu, H., Zijdenbos, A., Paus, T., Evans, A.C., Rapoport, J.L., 1999. Brain development during childhood and adolescence: a longitudinal MRI study. Nature Neuroscience 2, 861–863.
Glantz, L.A., Gilmore, J.H., Hamer, R.M., Lieberman, J.A., Jarskog, L.F., 2007. Synaptophysin and postsynaptic density protein 95 in the human prefrontal cortex from mid-gestation into early adulthood. Neuroscience 149, 582–591.
Glantz, L.A., Lewis, D.A., 2000. Decreased dendritic spine density on prefrontal cortical pyramidal neurons in schizophrenia. Archives of General Psychiatry 57, 65–73.
Gogtay, N., Giedd, J.N., Lusk, L., Hayashi, K.M., Greenstein, D., Vaituzis, A.C., Nugent 3rd, T.F., Herman, D.H., Clasen, L.S., Toga, A.W., Rapoport, J.L., Thompson, P.M., 2004. Dynamic mapping of human cortical development during childhood through early adulthood. Proceedings of the National Academy of Sciences of the United States of America 101, 8174–8179.
Gogtay, N., Thompson, P.M., 2010. Mapping gray matter development: implications for typical development and vulnerability to psychopathology. Brain and Cognition 72, 6–15.
Goldman-Rakic, P.S., 1994. Working memory dysfunction in schizophrenia. The Journal of Neuropsychiatry and Clinical Neurosciences 6, 348–357.
Goldman-Rakic, P.S., 1995. Cellular basis of working memory. Neuron 14, 477–485.
Goldman-Rakic, P.S., 1996. The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. Philosophical Transactions of the Royal Society B 351, 1445–1453.
Goldman-Rakic, P.S., 1999. The physiological approach: functional architecture of working memory and disordered cognition in schizophrenia. Biological Psychiatry 46, 650–661.
Goldman-Rakic, P.S., Brown, R.M., 1982. Postnatal development of monoamine content and synthesis in the cerebral cortex of rhesus monkeys. Brain Research 256, 339–349.
Goldman-Rakic, P.S., Leung, H.-C., 2002. Functional architecture of the dorsolateral prefrontal cortex in monkeys and humans. In: Stuss, D.T., Knight, R.T. (Eds.), Principles of Frontal Lobe Function. Oxford University Press, New York, pp. 85–95.
Goldman-Rakic, P.S., Muly 3rd, E.C., Williams, G.V., 2000. D(1) receptors in prefrontal cells and circuits. Brain Research 31, 295–301.
Gonzalez-Burgos, G., Kroener, S., Zaitsev, A.V., Povysheva, N.V., Krimer, L.S., Barrionuevo, G., Lewis, D.A., 2008. Functional maturation of excitatory synapses in layer 3 pyramidal neurons during postnatal development of the primate prefrontal cortex. Cerebral Cortex 18, 626–637.
Green, M.F., 1996. What are the functional consequences of neurocognitive deficits in schizophrenia? American Journal of Psychiatry 153, 321–330.

Hebb, D.O., 1949. The Organization of Behavior: A Neuropsychological Theory. Wiley, New York.
Hertz, J., Krogh, A., Palmer, R.G., 1991. An Introduction to the Theory of Neural Computation. Addison-Wesley, Wokingham.
Hopfield, J.J., 1982. Neural networks and physical systems with emergent collective computational abilities. Proceedings of the National Academy of Science of the United States of America 79, 2554–2558.
Irwin, I., DeLanney, L.E., McNeill, T., Chan, P., Forno, L.S., Murphy Jr., G.M., Di Monte, D.A., Sandy, M.S., Langston, J.W., 1994. Aging and the nigrostriatal dopamine system: a non-human primate study. Neurodegeneration 3, 251–265.
Jacobs, J., Kahana, M.J., Ekstrom, A.D., Fried, I., 2007. Brain oscillations control timing of single-neuron activity in humans. Journal of Neuroscience 27, 3839–3844.
Johnson, W., Logie, R.H., Brockmole, J.R., 2010. Working memory tasks differ in factor structure across age cohorts: Implications for dedifferentiation. Intelligence 38, 513–528.
Jucaite, A., Forssberg, H., Karlsson, P., Halldin, C., Farde, L., 2010. Age-related reduction in dopamine D1 receptors in the human brain: from late childhood to adulthood, a positron emission tomography study. Neuroscience 167, 104–110.
Kubota, K., Niki, H., 1971. Prefrontal cortical unit activity and delayed alternation performance in monkeys. Journal of Neurophysiology 34, 337–347.
Lewis, D.A., Cruz, D., Eggan, S., Erickson, S., 2004. Postnatal development of prefrontal inhibitory circuits and the pathophysiology of cognitive dysfunction in schizophrenia. Annals of the New York Academy of Sciences 1021, 64–76.
Lewis, D.A., Hashimoto, T., Volk, D.W., 2005. Cortical inhibitory neurons and schizophrenia. Nature Reviews 6, 312–324.
Lewis, D.A., Levitt, P., 2002. Schizophrenia as a disorder of neurodevelopment. Annual Review of Neuroscience 25, 409–432.
Liddle, P.F., 1987. The symptoms of chronic schizophrenia. A re-examination of the positive-negative dichotomy. The British Journal of Psychiatry 151, 145–151.
Lidow, M.S., Rakic, P., 1992. Scheduling of monoaminergic neurotransmitter receptor expression in the primate neocortex during postnatal development. Cerebral Cortex 2, 401–416.
Loh, M., Rolls, E.T., Deco, G., 2007a. A dynamical systems hypothesis of schizophrenia. PLoS Computational Biology 3, e228, 210.1371/journal.pcbi.0030228.
Loh, M., Rolls, E.T., Deco, G., 2007b. Statistical fluctuations in attractor networks related to schizophrenia. Pharmacopsychiatry 40, S78–S84.
Mueser, K.T., McGurk, S.R., 2004. Schizophrenia. Lancet 363, 2063–2072.
Paus, T., 2001. Primate anterior cingulate cortex: where motor control, drive and cognition interface. Nature Reviews Neuroscience 2, 417–424.
Rakic, P., 1996. Development of the cerebral cortex in human and nonhuman primates. In: Lewis, M.D. (Ed.), Child and Adolescent Psychiatry. Williams and Wilkins, Baltimore, MD, pp. 9–30.
Rakic, P., Bourgeois, J.P., Eckenhoff, M.F., Zecevic, N., Goldman-Rakic, P.S., 1986. Concurrent overproduction of synapses in diverse regions of the primate cerebral cortex. Science 232, 232–235.
Rakic, P., Bourgeois, J.P., Goldman-Rakic, P.S., 1994. Synaptic development of the cerebral cortex: implications for learning, memory, and mental illness. Progress in Brain Research 102, 227–243.
Ratcliff, R., Van Zandt, T., McKoon, G., 1999. Connectionist and diffusion models of reaction time. Psychological Reviews 106, 261–300.
Rolls, E.T., 1999. The Brain and Emotion. Oxford University Press, Oxford.
Rolls, E.T., 2005. Emotion Explained. Oxford University Press, Oxford.
Rolls, E.T., 2006. The neurophysiology and functions of the orbitofrontal cortex. In: Zald, D.H., Rauch, S.L. (Eds.), The Orbitofrontal Cortex. Oxford University Press, Oxford, pp. 95–124.
Rolls, E.T., 2008. Memory, Attention, and Decision-Making: A Unifying Computational Neuroscience Approach. Oxford University Press, Oxford.
Rolls, E.T., 2010a. A computational theory of episodic memory formation in the hippocampus. Behavioural Brain Research 205, 180–196.
Rolls, E.T., 2010b. Noise in the brain, decision-making, determinism, free will, and consciousness. In: Perry, E., Collerton, D., Ashton, H., Lebeau, F. (Eds.), New Horizons in the Neuroscience of Consciousness. John Benjamin, Amsterdam.
Rolls, E.T., Deco, G., 2002. Computational Neuroscience of Vision. Oxford University Press, Oxford.
Rolls, E.T., Deco, G., 2010. The Noisy Brain: Stochastic Dynamics as a Principle of Brain Function. Oxford University Press, Oxford.
Rolls, E.T., Grabenhorst, F., 2008. The orbitofrontal cortex and beyond: from affect to decision-making. Progress in Neurobiology 86, 216–244.
Rolls, E.T., Grabenhorst, F., Deco, G., 2010a. Choice, difficulty, and confidence in the brain. NeuroImage 53, 694–706.
Rolls, E.T., Grabenhorst, F., Deco, G., 2010b. Decision-making, errors, and confidence in the brain. Journal of Neurophysiology. Electronic publication 1 September.
Rolls, E.T., Loh, M., Deco, G., 2008a. An attractor hypothesis of obsessive-compulsive disorder. European Journal of Neuroscience 28, 782–793.
Rolls, E.T., Loh, M., Deco, G., Winterer, G., 2008b. Computational models of schizophrenia and dopamine modulation in the prefrontal cortex. Nature Reviews Neuroscience 9, 696–709.
Rolls, E.T., Treves, A., 1990. The relative advantages of sparse versus distributed encoding for associative neuronal networks in the brain. Network (Bristol, England) 1, 407–421.
Rolls, E.T., Treves, A., 1998. Neural Networks and Brain Function. Oxford University Press, Oxford.
Rosenberg, D.R., Lewis, D.A., 1995. Postnatal maturation of the dopaminergic innervation of monkey prefrontal and motor cortices: a tyrosine hydroxylase immunohistochemical analysis. The Journal of Comparative Neurology 358, 383–400.
Sawaguchi, T., Goldman-Rakic, P.S., 1991. D1 dopamine receptors in prefrontal cortex: involvement in working memory. Science 251, 947–950.
Sawaguchi, T., Goldman-Rakic, P.S., 1994. The role of D1-dopamine receptor in working memory: local injections of dopamine antagonists into the prefrontal cortex of rhesus monkeys performing an oculomotor delayed-response task. Journal of Neurophysiology 71, 515–528.
Sawaguchi, T., Matsumura, M., Kubota, K., 1988. Dopamine enhances the neuronal activity of spatial short-term memory task in the primate prefrontal cortex. Neuroscience Research 5, 465–473.
Sawaguchi, T., Matsumura, M., Kubota, K., 1990. Catecholaminergic effects on neuronal activity related to a delayed response task in monkey prefrontal cortex. Journal of Neurophysiology 63, 1385–1400.
Seamans, J.K., Durstewitz, D., Christie, B.R., Stevens, C.F., Sejnowski, T.J., 2001. Dopamine D1/D5 receptor modulation of excitatory synaptic inputs to layer V prefrontal cortex neurons. Proceedings of the National Academy of Sciences of the United States of America 98, 301–306.
Seamans, J.K., Yang, C.R., 2004. The principal features and mechanisms of dopamine modulation in the prefrontal cortex. Progress in Neurobiology 74, 1–58.
Seeman, P., Bzowej, N.H., Guan, H.C., Bergeron, C., Becker, L.E., Reynolds, G.P., Bird, E.D., Riederer, P., Jellinger, K., Watanabe, S., et al., 1987. Human brain dopamine receptors in children and aging adults. Synapse (New York, NY) 1, 399–404.
Seidman, L.J., Yurgelun-Todd, D., Kremen, W.S., Woods, B.T., Goldstein, J.M., Faraone, S.V., Tsuang, M.T., 1994. Relationship of prefrontal and temporal lobe MRI measures to neuropsychological performance in chronic schizophrenia. Biological Psychiatry 35, 235–246.
Smith, P.L., Ratcliff, R., 2004. Psychology and neurobiology of simple decisions. Trends in Neurosciences 27, 161–168.
Steinberg, L., 2005. Cognitive and affective development in adolescence. Trends in Cognitive Sciences 9, 69–74.
Swanson, H.L., 1999. What develops in working memory? A life span perspective. Developmental Psychology 35, 986–1000.
Treves, A., Rolls, E.T., 1991. What determines the capacity of autoassociative memories in the brain? Network (Bristol, England) 2, 371–397.
Vickers, D., 1979. Decision Processes in Visual Perception. Academic Press, New York.
Vijayraghavan, S., Wang, M., Birnbaum, S.G., Williams, G.V., Arnsten, A.F., 2007. Inverted-U dopamine D1 receptor actions on prefrontal neurons engaged in working memory. Nature Neuroscience 10, 376–384.
Wahlstrom, D., White, T., Luciana, M., 2010. Neurobehavioral evidence for changes in dopamine system activity during adolescence. Neuroscience and Biobehavioral Reviews 34, 631–648.
Wang, X.J., 2002. Probabilistic decision making by slow reverberation in cortical circuits. Neuron 36, 955–968.
Wang, X.J., 2006. Toward a prefrontal microcircuit model for cognitive deficits in schizophrenia. Pharmacopsychiatry 39 (Suppl. 1), S80–S87.
Wang, X.J., 2008. Decision making in recurrent neuronal circuits. Neuron 60, 215–234.
Weinberger, D.R., Berman, K.F., 1996. Prefrontal function in schizophrenia: confounds and controversies. Philosophical Transactions of the Royal Society of London 351, 1495–1503.
Williams, G.V., Goldman-Rakic, P.S., 1995. Modulation of memory fields by dopamine D1 receptors in prefrontal cortex. Nature 376, 572–575.
Winterer, G., Adams, C.M., Jones, D.W., Knutson, B., 2002. Volition to action—an event-related fMRI study. NeuroImage 17, 851–858.
Winterer, G., Coppola, R., Goldberg, T.E., Egan, M.F., Jones, D.W., Sanchez, C.E., Weinberger, D.R., 2004. Prefrontal broadband noise, working memory, and genetic risk for schizophrenia. The American Journal of Psychiatry 161, 490–500.
Winterer, G., Weinberger, D.R., 2004. Genes, dopamine and cortical signal-to-noise ratio in schizophrenia. Trends in Neurosciences 27, 683–690.
Winterer, G., Ziller, M., Dorn, H., Frick, K., Mulert, C., Wuebben, Y., Herrmann, W.M., Coppola, R., 2000. Schizophrenia: reduced signal-to-noise ratio and impaired phase-locking during information processing. Clinical Neurophysiology 111, 837–849.