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Review

Glutamate, obsessive–compulsive disorder, schizophrenia, and the stability of cortical attractor neuronal networks

Edmund T. Rolls

Oxford Centre for Computational Neuroscience, Oxford, UK

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ABSTRACT

A computational neuroscience approach to the symptoms of obsessive–compulsive disorder based on a stochastic neurodynamical framework is described. An increased depth in the basins of attraction of attractor neuronal network states in the brain makes each state too stable, so that it tends to remain locked in that state, and cannot easily be moved on to another state. It is suggested that the different symptoms that may be present in obsessive-–compulsive disorder could be related to changes of this type in different brain regions. In integrate-and-fire network simulations, an increase in the NMDA and/or AMPA receptor conductances, which increases the depth of the attractor basins, increases the stability of attractor networks, and makes them less easily moved on to another state by a new stimulus. Increasing GABA-receptor activated currents can partly reverse this overstability. There is now some evidence for overactivity in glutamate transmitter systems in obsessive–compulsive disorder, and the hypothesis presented here shows how some of the symptoms of obsessive–compulsive disorder could be produced by the increase in the stability of attractor networks that is produced by increased glutamatergic activity.

In schizophrenia, 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.

Contents

E-mail address: Edmund.Rolls@oxcns.org.
URL: http://www.oxcns.org.

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1. Introduction

In this paper, changes to the stability of cortical neuronal networks are described that provide approaches to understanding obsessive–compulsive disorder and schizophrenia, and possible treatments for them. For each disorder, I first describe a computational neuroscience approach, and then consider how glutamate is implicated in the changes in stability, and possible treatments.

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 (Rolls, 2008; Rolls and Deco, 2010b). 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, 2010b; Rolls and Deco, 2002, 2010b). This approach in turn leads to new approaches based on the stability of neurodynamical systems to some psychiatric disorders including obsessive–compulsive disorder and schizophrenia (Loh et al., 2007a, 2007b; Rolls and Deco, 2010a, Rolls et al., 2008c, 2008d), and to how changes in glutamate and glutamate receptor functioning may contribute to these disorders which is the special focus of this paper. This approach in turn leads to suggestions for treatments.

2. Obsessive–compulsive disorder

Obsessive–compulsive disorder (OCD) is a chronically debilitating disorder with a lifetime prevalence of 2–3% (Karno et al., 1988; Robins et al., 1984; Weissman et al., 1994). It is characterized by two sets of symptoms, obsessive and compulsive. Obsessions are unwanted, intrusive, recurrent thoughts or impulses that are often concerned with themes of contamination and 'germs', checking household items in case of fire or burglary, order and symmetry of objects, or fears of harming oneself or others. Compulsions are ritualistic, repetitive behaviors or mental acts carried out in relation to these obsessions e.g., washing, household safety checks, counting, rearrangement of objects in symmetrical array or constant checking of oneself and others to ensure no harm has occurred (Menzies et al., 2008). Patients with OCD experience the persistent intrusion of thoughts that they generally perceive as foreign and irrational but which cannot be dismissed. The anxiety associated with these unwanted and disturbing thoughts can be extremely intense; it is often described as a feeling that something is incomplete or wrong, or that terrible consequences will ensue if specific actions are not taken. Many patients engage in repetitive, compulsive behaviors that aim to discharge the anxieties associated with these obsessional thoughts. Severely affected patients can spend many hours each day in their obsessional thinking and resultant compulsive behaviors, leading to marked disability (Pittenger et al., 2006).

While OCD patients exhibit a wide variety of obsessions and compulsions, the symptoms tend to fall into specific clusters. Common patterns include obsessions of contamination, with accompanying cleaning compulsions; obsessions with symmetry or order, with accompanying ordering behaviors; obsessions of saving, with accompanying hoarding; somatic obsessions; aggressive obsessions with checking compulsions; and sexual and religious obsessions (Pittenger et al., 2006).

Here I review and update a computational neuroscience theory of how obsessive–compulsive disorders arise, and of the different symptoms (Rolls et al., 2008c). The theory is based on the top-down proposal that there is overstability of attractor neuronal networks in cortical and related areas in obsessive–compulsive disorders. The approach is top-down in that it starts with the set of symptoms and maps them onto the dynamical systems framework, and only after this considers detailed underlying biological mechanisms, of which there could be many, that might produce the effects. (In contrast, a complementary bottom-up approach starts from detailed neurobiological mechanisms, and aims to interpret their implications with a brain-like model for higher level phenomena.) Integrate-and-fire neuronal network simulations show that the overstability could arise by for example overactivity in glutamatergic excitatory neurotransmitter synapses, which produces an increased depth of the basins of attraction, in the presence of which neuronal spiking-related and potentially other noise are insufficient to help the system move out of an attractor basin. I relate this top-down proposal, related to the stochastic dynamics of neuronal networks, to new evidence that there may be overactivity in glutamatergic systems in obsessive-compulsive disorders, and consider the implications for treatment.

2.1. Attractor networks, and their stability

The attractor framework is based on dynamical systems theory. In a network of interconnected neurons, a memory pattern (represented by a set of active neurons) can be stored by synaptic modification, and later recalled by external inputs. Furthermore, a pattern activated by an input is then stably maintained by the system even after input offset. These patterns could correspond to memories, perceptual representations, or thoughts (Rolls, 2008; Rolls and Deco, 2010b).

The architecture of an attractor or autoassociation network is as follows (see Fig. 1a). 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 to each other 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 implemented 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). The inhibitory interneurons are not shown. They receive inputs from the pyramidal cells, and make inhibitory negative feedback connections onto the pyramidal cells to keep their activity under control. Hopfield (1982) showed that the recall state in a simple attractor network can be thought of as the

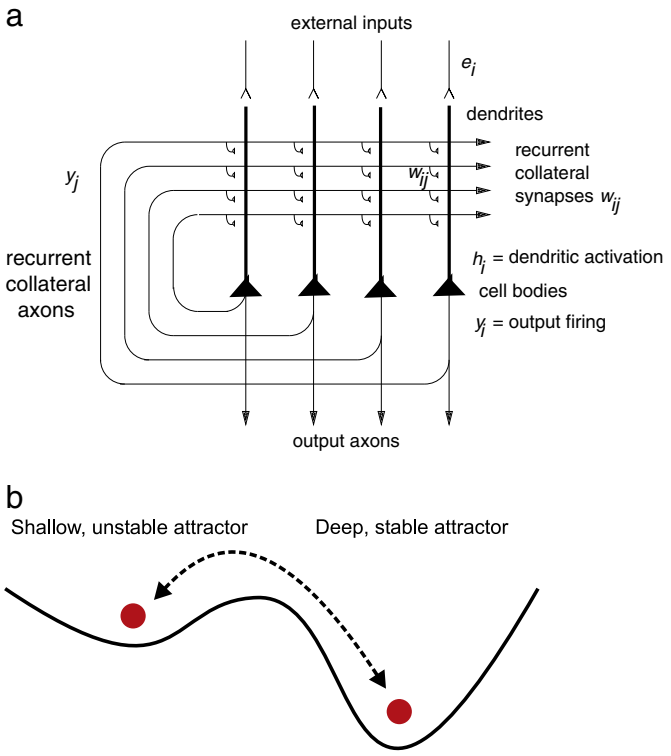

Fig. 1. (a) Architecture of an attractor network. External inputs e_i activate the neurons in the network, and produce firing y_i, where i refers to the i'th neuron. The neurons are connected by recurrent collateral synapses w_{ij}, where j refers to the j'th synapse on a neuron. By these synapses an 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 be formed by an associative (Hebbian) learning mechanism. 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. (b) Energy landscape. The first basin (from the left) in the energy landscape is the spontaneous state, and the second basin is the high firing rate attractor state, which is 'persistent' in that the neurons that implement it continue firing. The vertical axis of the landscape is the energy potential. The horizontal axis is the firing rate, with high to the right. In the normal condition, the valleys for both the spontaneous and for the high firing attractor state are equally deep, making both states stable. In the situation that is hypothesized to be related to some of the symptoms of obsessive compulsive disorder, the basin for the high firing attractor state is deep, making the high firing rate attractor state that implements for example short term memory too stable, and very resistant to distraction. This increased depth of the basin of attraction of the persistent state may be associated with higher firing rates of the neurons, if for example the state is produced by increased currents in NMDA receptors. In general, there will be many different high firing rate attractor basins, each corresponding to a different memory.

local minimum in an energy landscape, where the energy would be defined as

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

where < .. > indicates the ensemble average. The concept is that a particular attractor implemented by a subset of the neurons in a network will have a low energy, and be stable, if the neurons i and j within the attractor are connected by strong synaptic weights w_{ij} and have high firing rates y_i and y_j. Autoassociation attractor systems have two types of stable fixed points: a spontaneous state with a low firing rate, and one or more attractor states with high firing rates in which the positive feedback implemented by the recurrent collateral connections maintains a high firing rate. We sometimes refer to this latter state as the persistent state (see S and P in Fig. 6). The area in the energy landscape within which the system will move to a stable attractor state is called its basin of attraction.

The attractor dynamics can be pictured by energy landscapes, which indicate the basin of attraction by valleys, and the attractor states or fixed points by the bottom of the valleys. (Although energy functions apply to recurrent networks with symmetric connections between the neurons (Hopfield, 1982) as would be the case in a fully connected network with associative synaptic modification, and do not necessarily apply to more complicated networks with for example incomplete connectivity, nevertheless the properties of these other recurrent networks are similar (Rolls and Treves, 1998; Treves, 1991; Treves and Rolls, 1991), and the concept of an energy function and landscape is useful for discussion purposes. In practice, a Lyapunov function can be used to prove analytically that there is a stable fixed point such as an attractor basin (Khalil, 1996), and even in systems where this cannot be proved analytically, it may still be possible to show numerically that there are stable fixed points, to measure the flow towards those fixed points which describes the depth of the attractor basin as we have done for this type of network (Loh et al., 2007a), and to use the concept of energy or potential landscapes to help visualize the properties of the system.) 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. The noise provokes transitions to other attractor states. One source of noise results from the interplay between the Poissonian character of the spikes and the finite-size effect due to the limited number of 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. 1b), then less force is needed to move a ball from one valley to the next. Second, high noise will make it more likely 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. The noise could arise not only from the probabilistic spiking of the neurons which has significant effects in finite size integrate-and-fire networks (Deco and Rolls, 2006; Rolls, 2008; Rolls and Deco, 2010b), but also from any other source of noise in the brain or the environment (Faisal et al., 2008), including the effects of distracting stimuli.

2.2. A hypothesis about the increased stability of attractor networks and the symptoms of obsessive-compulsive disorder

The hypothesis is that cortical and related attractor networks become too stable in obsessive–compulsive disorder, so that once in an attractor state, the networks tend to remain there too long (Rolls et al., 2008c). The hypothesis is that the depths of the basins of attraction become deeper, and that this is what makes the attractor networks more stable. I further hypothesize that part of the mechanism for the increased depth of the basins of attraction is increased glutamatergic transmission, which increases the depth of the basins of attraction by increasing the firing rates of the neurons, and by increasing the effective value of the synaptic weights between the associatively modified synapses that define the attractor, as is made evident in Eq. (1) above. The synaptic strength is effectively increased if more glutamate is released per action potential at the synapse, or if in other ways the currents injected into the neurons through the NMDA (N-methyl-d-aspartate) and/or AMPA synapses are larger. In addition, if NMDA receptor function is increased, this could also increase the stability of the system because of the temporal smoothing effect of the long time constant of the NMDA receptors (Wang, 1999).

This increased stability of cortical and related attractor networks, and the associated higher neuronal firing rates, could occur in different brain regions, and thereby produce different symptoms, as follows.

If these effects occurred in high order motor areas, the symptoms could include inability to move out of one motor pattern, resulting for

example in repeated movements or actions. In parts of the cingulate cortex and dorsal medial prefrontal cortex, this could result in difficulty in switching between actions or strategies (Rushworth et al., 2007a, 2007b), as the system would be locked into one action or strategy. If an action was locked into a high order motor area due to increased stability of an attractor network, then lower order motor areas might thereby not be able to escape easily what they implement, such as a sequence of movements, so that the sequence would be repeated.

A similar account, of becoming locked in one action and having difficulty in switching to another action, can be provided for response inhibition deficits, which have been found in OCD. The response inhibition deficit has been found in tasks such as go/no-go and stop-signal reaction time (SSRT) which examine motor inhibitory processes, and also the Stroop task, a putative test of cognitive inhibition (Bannon et al., 2002, 2006; Chamberlain et al., 2006, 2007; Hartston and Swerdlow, 1999; Penades et al., 2005, 2007). For example, response inhibition deficits have been reported in OCD patients when performing the SSRT, which measures the time taken to internally suppress pre-potent motor responses (Chamberlain et al., 2006). Unaffected first-degree relatives of OCD patients are also impaired on this task compared with unrelated healthy controls, suggesting that response inhibition may be an endophenotype (or intermediate phenotype) for OCD (Chamberlain et al., 2007; Menzies et al., 2008).

If occurring in the lateral prefrontal cortex (including the dorsolateral and ventrolateral parts), the increased stability of prefrontal attractor networks, which provide the basis for short-term memory and thereby provide the source of the top-down bias in biased competition and biased activation theories of attention (Deco and Rolls, 2003, 2005a; Desimone and Duncan, 1995; Ge et al., 2011; Grabenhorst and Rolls, 2010; Rolls, 2008; Stemme et al., 2007), could produce symptoms that include a difficulty in shifting attention and in cognitive set shifting. These are in fact important symptoms that can be found in obsessive–compulsive disorder (Menzies et al., 2008). These have been concerned with two quite different forms of shift: affective set shifting, where the affective or reward value of a stimulus changes over time (e.g., a rewarded stimulus is no longer rewarded) (intradimensional or ID set shifting); and attentional set shifting, where the stimulus dimension (e.g., shapes or colors) to which the subject must attend is changed (extradimensional or ED set shifting). Deficits of attentional set shifting in OCD have been found in several neurocognitive studies using the CANTAB ID/ED set shifting task (Chamberlain et al., 2006, 2007; Veale et al., 1996; Watkins et al., 2005). This deficit is most consistently reported at the ED stage (in which the stimulus dimension, e.g., shape, color or number, alters and subjects have to inhibit their attention to this dimension and attend to a new, previously irrelevant dimension). The ED stage is analogous to the stage in the Wisconsin Card Sorting Task where a previously correct rule for card sorting is changed and the subject has to respond to the new rule (Berg, 1948). This ED shift impairment in OCD patients is considered to reflect a lack of cognitive or attentional flexibility and may be related to the repetitive nature of OCD symptoms and behaviors. Deficits in attentional set shifting are considered to be more dependent upon dorsolateral and ventrolateral prefrontal regions than the orbital prefrontal regions included in the orbito-fronto-striatal model of OCD (Hampshire and Owen, 2006; Nagahama et al., 2001; Pantelis et al., 1999; Rogers et al., 2000), suggesting that cognitive deficits in OCD may not be underpinned exclusively by orbitofrontal cortex pathology. Indeed, intradimensional or affective set shifting may not be consistently impaired in OCD (Menzies et al., 2008).

Planning may also be impaired in patients with OCD (Menzies et al., 2008), and this could arise because there is too much stability of attractor networks in the dorsolateral prefrontal cortex concerned with holding in mind the different short term memory representations that encode the different steps of a plan (Rolls, 2008). Indeed, there is evidence for dorsolateral prefrontal cortex (DLPFC) dysfunction in patients with OCD, in conjunction with impairment on a version of the Tower of London, a task often used to probe planning aspects of executive function (van den Heuvel et al., 2005). Impairment on the Tower of London task has also been demonstrated in healthy first-degree relatives of OCD patients (Delorme et al., 2007).

An increased firing rate of neurons in the orbitofrontal cortex, and anterior cingulate cortex, produced by hyperactivity of glutamatergic transmitter systems, would increase emotionality, which is frequently found in obsessive–compulsive disorder. Part of the increased anxiety found in obsessive–compulsive disorder could be related to an inability to complete tasks or actions in which one is locked. But part of my unifying proposal is that part of the increased emotionality in OCD may be directly related to increased firing produced by the increased glutamatergic activity in brain areas such as the orbitofrontal and anterior cingulate cortex. The orbitofrontal cortex and anterior cingulate cortex are involved in emotion, in that they are activated by primary and secondary reinforcers that produce affective states (Grabenhorst and Rolls, 2011; Rolls, 2004, 2005, 2009a; Rolls and Grabenhorst, 2008), for example with activations proportional to the magnitude of subjective pleasantness/unpleasantness (Grabenhorst and Rolls, 2009; Grabenhorst et al., 2008, 2010a, 2010b; Rolls et al., 2008a, 2008b), and in that damage to these regions alters emotional behavior and emotional experience (Hornak et al., 2003, 1996; Rolls et al., 1994). Indeed, negative emotions as well as positive emotions activate the orbitofrontal cortex, with the emotional states produced by negative events tending to be represented in the lateral orbitofrontal cortex and dorsal part of the anterior cingulate cortex (Grabenhorst and Rolls, 2011; Kringelbach and Rolls, 2004; Rolls, 2005, 2009a; Rolls and Grabenhorst, 2008). Although the point here is that the increased firing per se associated with hyperglutamatergia would increase emotionality, this could in turn lead to more stable attractors in this region, which given that they are likely to implement on-going mood states (Rolls, 2005), would tend to make mood states prolonged and stubborn to change. We may note that stimulus-reinforcer reversal tasks (also known as intra-dimensional shifts or affective reversal) are not generally impaired in patients with OCD (Menzies et al., 2008).

If the increased stability of attractor networks occurred in temporal lobe semantic memory networks, then this would result in a difficulty in moving from one thought to another, and possibly in stereotyped thoughts, which again may be a symptom of obsessive–compulsive disorder (Menzies et al., 2008).

The obsessional states are thus proposed to arise because cortical areas concerned with cognitive functions have states that become too stable. The compulsive states are proposed to arise partly in response to the obsessional states, but also partly because cortical areas concerned with actions have states that become too stable. The theory provides a unifying computational account of both the obsessional and compulsive symptoms, in that both arise due to increased stability of cortical attractor networks, with the different symptoms related to overstability in different cortical areas. The theory is also unifying in that a similar increase in glutamatergic activity in the orbitofrontal and far anterior cingulate cortex could increase emotionality, as described above.

2.3. Alterations to glutamatergic transmitter systems that may increase the depth of the basins of attraction of cortical and related attractor networks

To demonstrate how alterations of glutamate as a transmitter for the connections between the neurons may influence the stability of attractor networks, we performed integrate-and-fire simulations (Rolls et al., 2008c). A feature of these simulations is that we simulated the currents produced by activation of NMDA and AMPA receptors in the recurrent collateral synapses, and took into account

the effects of the spiking-related noise, which is an important factor in determining whether the attractor stays in a basin of attraction, or jumps over an energy barrier into another basin (Loh et al., 2007a). These attractors are likely to be implemented in many parts of the cerebral cortex by the recurrent collateral connections between pyramidal cells, and have short term memory properties with basins of attraction that allow systematic investigation of stability and distractibility. The particular neural network implementation we adopt includes channels activated by AMPA, NMDA and $GABA_A$ receptors and allows not only the spiking activity to be simulated, but also a consistent mean-field approach to be used (Brunel and Wang, 2001). The mean-field approach allows the values of the synaptic strengths in the simulation to be determined in such a way that the network is stable and implements for example short-term memory of decision-making in the absence of noise (Brunel and Wang, 2001; Deco and Rolls, 2006; Rolls and Deco, 2010b). The neuronal and synaptic parameters were chosen to be biologically accurate, and the network forms a useful model of cortical processing for short-term memory, attention, and decision-making, with predictions from the model being validated by for example fMRI investigations (Deco and Rolls, 2003, 2005b, 2006; Rolls and Deco, 2010b; Rolls et al., 2010a, 2010b).

We used a minimal architecture, a single attractor or autoassociation network (Amit, 1989; Hertz et al., 1991; Hopfield, 1982; Rolls and Deco, 2002; Rolls and Treves, 1998). We chose a recurrent (attractor) integrate-and-fire network model which includes synaptic channels for AMPA, NMDA and $GABA_A$ receptors (Brunel and Wang, 2001). The integrate-and-fire model is necessary to characterize and exploit the effects of the spiking noise produced by the neurons in a finite-sized network. However, to initialize the parameters of the integrate-and-fire model such as the synaptic connection strengths to produce stable attractors, and to ensure that the spontaneous activity is in the correct range, we used a mean-field approximation consistent with the integrate-and-fire network (Rolls et al., 2008c).

Both excitatory and inhibitory neurons are represented by a leaky integrate-and-fire model (Tuckwell, 1988). The basic state variable of a single model neuron is the membrane potential. It decays in time when the neurons receive no synaptic input down to a resting potential. When synaptic input causes the membrane potential to reach a threshold, a spike is emitted and the neuron is set to the reset potential at which it is kept for the refractory period. The emitted action potential is propagated to the other neurons in the network. The excitatory neurons transmit their action potentials via the AMPA and NMDA glutamatergic receptors which are both modeled by their effect in producing exponentially decaying currents in the postsynaptic neuron. The rise time of the AMPA current is neglected, because it is typically very short. The NMDA channel is modeled with an alpha function including both a rise and a long decay term. In addition, the synaptic function of the NMDA current includes a voltage dependence controlled by the extracellular magnesium concentration (Jahr and Stevens, 1990). The inhibitory postsynaptic potential is mediated by a $GABA_A$ receptor model and is described by a decay term.

The single attractor network contains 400 excitatory and 100 inhibitory neurons, which is consistent with the observed proportions of pyramidal cells and interneurons in the cerebral cortex (Abeles, 1991; Braitenberg and Schütz, 1991). The connection strengths are adjusted using mean-field analysis (Brunel and Wang, 2001), so that the excitatory and inhibitory neurons exhibit a spontaneous activity of 3 Hz and 9 Hz, respectively (Koch and Fuster, 1989; Wilson et al., 1994). The recurrent excitation mediated by the AMPA and NMDA receptors is dominated by the long time constant NMDA currents to avoid instabilities during the delay periods (Wang, 1999, 2002).

Our cortical network model features a minimal architecture to investigate stability and distractibility, and consists of two selective pools S1 and S2 (Fig. 2a). We used just two selective pools to eliminate possible disturbing factors. Pool S1 is used for the short term memory item to be remembered, sometimes called the target; and pool S2 is used for the distractor. The non-selective pool NS models the spiking of cortical neurons and serves to generate an approximately Poisson spiking dynamics in the model (Brunel and Wang, 2001), which is what is observed in the cortex. The inhibitory pool IH contains the 100 inhibitory neurons. There are thus four populations or pools of neurons in the network, and the connection weights are set up as described next using a mean-field analysis to make S1 and S2 have stable attractor properties. The connection weights between the neurons of each selective pool or population are called the intra-pool connection strengths w_+. The increased strength of the intra-pool connections is counterbalanced by the other excitatory connections (w_-) to keep the average input to a neuron constant.

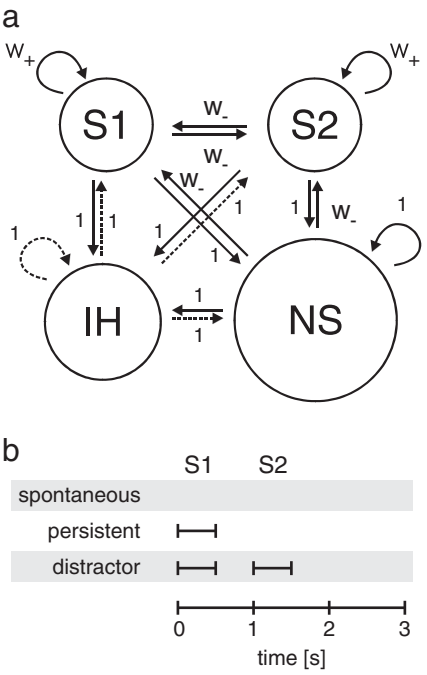

Fig. 2. (a) The attractor network model. The excitatory neurons are divided into two selective pools S1 and S2 (with 40 neurons each) with strong intra-pool connection strengths w_+ and one non-selective pool (NS) (with 320 neurons). The other connection strengths are 1 or weak w_-. The network contains 500 neurons, of which 400 are in the excitatory pools and 100 are in the inhibitory pool IH. The network also receives inputs from 800 external neurons, and these neurons increase their firing rates to apply a stimulus or distractor to one of the pools S1 or S2. The synaptic connection matrices are provided elsewhere (Rolls et al., 2008c). (b) The simulation protocols. Stimuli to either the S1 or S2 population of neurons are applied at different times depending on the type of simulations. The spontaneous simulations include no input. The persistent simulations assess how stably a stimulus is retained by the network. The distractor simulations add a distractor stimulus to further address the stability of the network activity, when it has been started by S1.

The network receives Poisson input spikes via AMPA receptors which are envisioned to originate from 800 external neurons at an average spontaneous firing rate of 3 Hz from each external neuron, consistent with the spontaneous activity observed in the cerebral cortex (Rolls and Treves, 1998; Wilson et al., 1994). A detailed mathematical description and all the equations are provided elsewhere (Rolls et al., 2008c).

We simulated three different conditions: the spontaneous, persistent, and distractor conditions (see Fig. 2b).

In spontaneous simulations, we run spiking simulations for 3 s without any extra external input. The aim of this condition is to test whether the network is stable in maintaining a low average firing rate in the absence of any inputs, or whether it falls into one of its attractor states without any external input.

In persistent simulations, an external cue of 120 Hz above the background firing rate of 2400 Hz is applied to each neuron in pool S1 during the first 500 ms to induce a high activity state and then the system is run for another 2.5 s. The 2400 Hz is distributed across the 800 synapses of each S1 neuron for the external inputs, with the spontaneous Poisson spike trains received by each synapse thus having a mean rate of 3 Hz. The aim of this condition is to investigate whether once in an attractor short term memory state, the network can maintain its activity stably, or whether it falls out of its attractor, which might correspond to an inability to maintain attention.

The distractor simulations start off like the persistent simulations with a 500 ms input to pool S1 to start the S1 short term memory attractor state, but between 1 s and 1.5 s we apply a distracting input to pool S2 with varying strengths. The aim of this condition is to measure how distractible the network is. The degree of distractibility is measured parametrically by the strength of the input to S2 required to remove the high activity state of the S1 population. These simulation protocols serve to assess the generic properties of the dynamical attractor system rather than to model specific experimental data obtained in particular paradigms.

The mean-field approach was used to calculate the synaptic weights to set the normal conditions for the operation of the network to be as follows (Rolls et al., 2008c). For the spontaneous state, the conditions for the numerical simulations of the mean-field method were set to 3 Hz for all excitatory pools and 9 Hz for the inhibitory pool. These values correspond to the approximate values of the spontaneous attractors when the network is not driven by stimulus-specific inputs. For the persistent state, a selective pool was set to a higher initial value (30 Hz) to account for the excitation of these neurons during the preceding cue period.

To clarify the concept of stability, examples of trials of spontaneous and persistent simulations in which the statistical fluctuations have different impacts on the temporal dynamics are shown in Fig. 3, as follows.

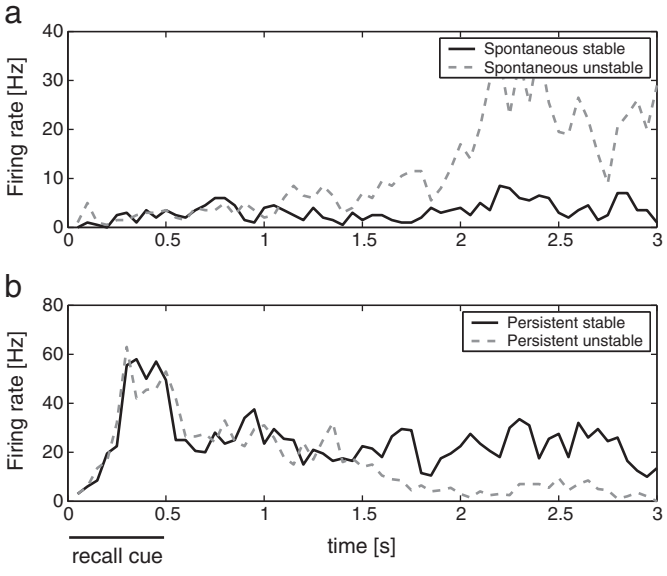

Fig. 3. Example trials of the integrate-and-fire attractor network simulations of short-term memory. The average firing rate of all the neurons in the S1 neuronal population (or pool) is shown. (a) Performance without a recall cue. The spontaneous firing rate is maintained at a low rate correctly on most trials (spontaneous stable), but on some trial the spiking-related noise in the network triggers the S1 population of neurons into a high firing rate state (spontaneous unstable), which is incorrect. (b) Performance with a recall cue applied to S1 at 0–500 ms. In the stable persistent type of trial, the firing continues or persists at a moderate rate throughout the trial after the end of the recall cue (persistent stable), and this is correct. On some trials the spiking-related noise provokes a transition to the low firing rate state, and this is incorrect (persistent unstable). In these simulations the network parameter was $w_+ = 2.1$.

In the spontaneous state simulations, no cue is applied, and we are interested in whether the network remains stably in the spontaneous firing state, or whether it is unstable and on some trials due to statistical fluctuations enters one of the attractors, thus falsely retrieving a memory. Fig. 3a shows an example of a trial on which the network correctly stays in the low spontaneous firing rate regime (spontaneous stable), and another trial (labeled spontaneous unstable) in which statistical spiking-related fluctuations in the network cause it to enter incorrectly a high activity state, moving into one of the attractors even without a stimulus.

In the persistent state simulations, a strong excitatory input is given to the S1 neuronal population between 0 and 500 ms. Two such trials are shown in Fig. 3b. In the 'persistent stable' trial the S1 neurons (correctly) keep firing at approximately 30 Hz after the retrieval cue is removed at 500 ms. However, on the 'persistent unstable' trial due to statistical fluctuations in the network related to the spiking activity, the high firing rate in the attractor for S1 was not stable, and the firing decreased back towards the spontaneous level, in the example shown starting after 1.5 s. This trial illustrates the failure to maintain a stable short term memory state, even when no distractor is applied.

In Fig. 3 the transitions to the incorrect activity states are caused by statistical fluctuations in the spiking activity of the integrate-and-fire neurons. I hypothesize that the stability of the high firing rate 'persistent' attractor state may be increased in obsessive compulsive disorder, and that in addition the spontaneous state may be less likely to remain low, but may jump into a high firing rate attractor state. I note that there are two sources of noise in the spiking networks that cause the statistical fluctuations: the randomly arriving external Poisson spike trains, and the statistical fluctuations caused by the spiking of the neurons in the finite sized network. The magnitude of these fluctuations increases as the number of neurons in the network becomes smaller (Mattia and Del Giudice, 2004; Rolls and Deco, 2010b).

For our investigations, we selected $w_+ = 2.1$, which with the default values of the NMDA and GABA conductances yielded stable dynamics, that is, a stable spontaneous state if no retrieval cue was applied, and a stable state of persistent firing after a retrieval cue had been applied and removed. To investigate the effects of changes (modulations) in the NMDA, AMPA and GABA conductances, we chose for demonstration purposes increases of 3% for the NMDA, and 10% for the AMPA and GABA synapses between the neurons in the network shown in Fig. 2a, as these were found to be sufficient to alter the stability of the attractor network. A strength of our approach is that we show that even quite small increases in the synaptic currents can alter the global behavior of the network, e.g. the stability of its attractors.

We assessed how the stability of both the spontaneous and persistent states changes when NMDA and AMPA efficacies are modulated. Specifically we ran multiple trial integrate-and-fire network simulations and counted how often the system maintained the spontaneous or persistent state, assessed by the firing rate in the last second of the simulation (2–3 s) of each 3 s trial. We showed that for the persistent run simulations, in which the cue triggered the attractor into the high firing rate attractor state, the network was still in the high firing rate attractor state in the baseline condition on approximately 88% of the runs, and that this had increased to 98% when the NMDA conductances were increased by 3% (+NMDA) (Fig. 4). Thus increasing the NMDA receptor-activated synaptic currents increased the stability of the network. Further, increasing AMPA by 10% (+AMPA) could also increase the stability of the persistent high firing rate attractor state, as did the combination +NMDA+AMPA (Rolls et al., 2008c).

Fig. 4 shows that in the baseline condition the spontaneous state was unstable on approximately 10% of the trials, that is, on 10% of the trials the spiking noise in the network caused the network run in the condition without any initial retrieval cue to end up in a high firing

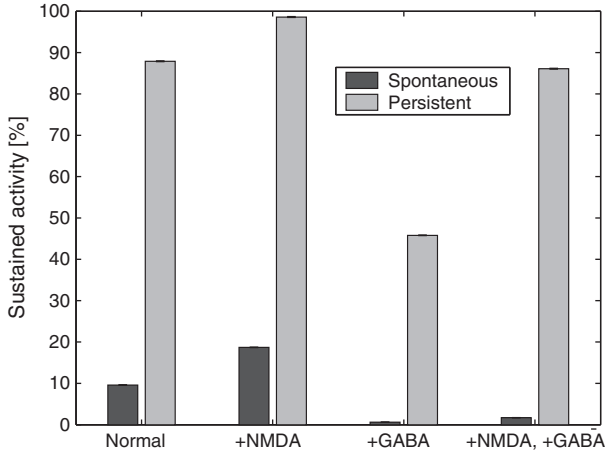

Fig. 4. The effect of increasing GABA-receptor mediated synaptic conductances by 10% (+GABA) on the stability of the network. The percent (%) of the simulation runs on which the network during the last second of the 3 s simulation was in the high firing rate attractor state is shown on the ordinate. For the persistent run simulations, in which the cue triggered the attractor into the high firing rate attractor state, the network was still in the high firing rate attractor state in the baseline condition on approximately 88% of the runs, and this increased to nearly 100% when the NMDA conductances were increased by 3% (+NMDA). The effect was highly significant as assessed with the binomial distribution, with the means ± sem shown (for details see (Rolls et al., 2008c)). For the spontaneous state simulations, in the baseline condition the spontaneous state was unstable on approximately 10% of the trials, that is, on 10% of the trials the spiking noise in the network caused the network run in the condition without any initial retrieval cue to end up in a high firing rate attractor state. In the +NMDA condition, the spontaneous state had jumped to the high firing rate attractor state on 25% of the runs, that is the low firing rate spontaneous state was present at the end of a simulation on only approximately 75% of the runs. Increasing the GABA currents by 10% when the NMDA currents are increased by 3% (+NMDA+GABA) moved the persistent state away from the overstability produced by +NMDA alone, and returned the persistent state to the normal baseline level. That is, instead of the system ending up in the high firing rate attractor state in the persistent state simulations on 98% of the runs in the +NMDA condition, the system ended up in the high firing rate attractor state on approximately 88% of the runs in the +NMDA+GABA condition. The combination +NMDA+GABA produced a spontaneous state that was less likely than the normal state to jump to a high firing rate attractor.

rate attractor state. This is of course an error that is related to the spiking noise in the network. In the +NMDA condition, the spontaneous state had jumped to the high firing rate attractor state on approximately 22% of the runs, that is the low firing rate spontaneous state was present at the end of a simulation on only approximately 78% of the runs. Thus increasing NMDA receptor activated currents can contribute to the network jumping from what should be a quiescent state of spontaneous activity into a high firing rate attractor state. We relate this to the symptoms of obsessive–compulsive disorders, in that the system can jump into a state with a dominant memory (which might be an idea or concern or action) even when there is no initiating input. The condition +AMPA can make the spontaneous state more likely to jump to a persistent high firing rate attractor state, as can the combination +NMDA+AMPA (Rolls et al., 2008c).

We next investigated to what extent alterations of the GABA-receptor mediated inhibition in the network could restore the system towards more normal activity even when NMDA and/or AMPA conductances were high. Fig. 4 shows that increasing the GABA currents by 10% when the NMDA currents are increased by 3% (+NMDA+GABA) can move the persistent state away from over-stability back to the normal baseline state. That is, instead of the system ending up in the high firing rate attractor state in the persistent state simulations on 98% of the runs, the system ended up in the high firing rate attractor state on approximately 88% of the runs, the baseline level. Increasing GABA has a large effect on the stability of the spontaneous state, making it less likely to jump to a high firing rate attractor state. The combination +NMDA+GABA produced a spontaneous state in which the +GABA overcorrected for the effect of +NMDA. That is, in the +NMDA+GABA condition the network was very likely to stay in the spontaneous firing rate condition in which it was started, or, equivalently, when tested in the spontaneous condition, the network was less likely than normal to jump to a high firing rate attractor. Increasing GABA thus corrected for the effect of increasing NMDA receptor activated synaptic currents on the persistent type of run when there was an initiating stimulus; and overcorrected for the effect of increasing NMDA on the spontaneous state simulations when there was no initiating retrieval stimulus, and the network should remain in the low firing rate state until the end of the simulation run. The implications for symptoms are that agents that increase GABA conductances might reduce and normalize the tendency to remain locked into an idea or concern or action; and would make it much less likely that the quiescent resting state would be left by jumping because of the noisy spiking towards a state representing a dominant idea or concern or action. The effects of increasing GABA receptor activated currents alone was to make the persistent simulations less stable (less likely to end in a high firing rate state), and the spontaneous simulations to be more stable (more likely to end up in the spontaneous state).

We next investigated how an increase of NMDA currents might make the system less distractible, and overstable in remaining in an attractor. This was investigated as shown in Fig. 2b by setting up a system with two high firing rate attractors, S1 and S2, then starting the network in an S1 attractor state with S1 applied at t = 0–0.5 s, and then applying a distractor S2 at time t = 1–1.5 s to investigate how strong S2 had to be to distract the network out of its S1 attractor. We found that in the +NMDA condition the system is more stable in its high firing rate attractor, and less able to be moved to another state by another stimulus (in this case S2). We relate this to the symptoms of obsessive–compulsive disorder, in that once in an attractor state (which might reflect an idea or concern or action), it is very difficult to get the system to move to another state. Increasing AMPA receptor activated synaptic currents (by 10%, +AMPA) produces similar, but smaller, effects (Rolls et al., 2008c).

We also showed that increasing GABA activated synaptic conductances (by 10%, +GABA) can partly normalize the overstability and decrease of distractibility that is produced by elevating NMDA receptor activated synaptic conductances (by 3%, +NMDA) (Rolls et al., 2008c).

2.4. Glutamate transmission in the light of this computational approach to OCD

This is a new approach to the symptoms of obsessive–compulsive disorder, for it deals with the symptoms in terms of overstability of attractor networks in the cerebral cortex. If the same generic change in stability were produced in different cortical areas, then we have indicated how different symptoms might arise. Of course, if these changes were more evident in some areas than in others in different patients, this would help to account for the different symptoms in different patients. Having proposed a generic hypothesis for the disorder, we recognize of course that the exact symptoms that arise if stability in some systems is increased will be subject to the exact effects that these will have in an individual patient, who may react to these effects, and produce explanatory accounts for the effects, and ways to deal with them, that may be quite different from individual to individual.

2.4.1. Increases in glutamatergic function in OCD

The simulation evidence, that an increase of glutamatergic synaptic efficacy can increase the stability of attractor networks and thus potentially provide an account for some of the symptoms of obsessive–compulsive disorder, is consistent with evidence that glutamatergic function may be increased in some brain systems in

obsessive–compulsive disorder (Pittenger et al., 2006; Rosenberg et al., 2000, 2001, 2004) and that cerebro-spinal-fluid glutamate levels are elevated (Chakrabarty et al., 2005). Some of the brain systems in which this increase in glutamatergic activity is found are the orbitofrontal cortex (Whiteside et al., 2006) and striatum (Rosenberg et al., 2000), though not the anterior cingulate cortex (Rotge et al., 2010). Rosenberg et al. (2000) have shown that glutamatergic concentrations within the caudate nucleus decreased to levels comparable with those of control subjects after 12 weeks of serotonin reuptake inhibitor (SRI) treatment, in parallel with OCD symptom severity. Therefore, the anti-obsessive-compulsive effects of SRIs might be related to their ability to modulate glutamatergic concentrations. In a rodent study, the SRI fluoxetine was found to decrease the expression of the excitatory amino acid transporter (EAAT2), providing a possible mechanism for SRIs to decrease glutamatergic function (Zink et al., 2011). Further, although SRIs are commonly used in the treatment of OCD (Denys, 2006), approximately 30% of cases do not respond to the treatment (Goddard et al., 2008), so alternatives related to glutamate neurotransmission are of interest.

2.4.2. Gene-based effects in OCD

Further evidence for a link between glutamate as a neurotransmitter and OCD comes from genetic studies. There is evidence for a significant association between the SLC1A1 glutamate transporter gene and OCD (Arnold et al., 2009, 2006; Pauls, 2010; Shugart et al., 2009; Stewart et al., 2007). This transporter is crucial in terminating the action of glutamate as an excitatory neurotransmitter and in maintaining extracellular glutamate concentrations within a normal range (Bhattacharyya and Chakraborty, 2007). SLC1A1 codes for the glutamate transporter EAAC-1 (excitatory amino acid carrier-1) (Rotge et al., 2010; Shugart et al., 2009), which contributes to the regulation of glutamatergic neurotransmission by maintaining low extracellular glutamate levels. A reduced efficacy of this gene might lead to increased glutamate levels in the neocortex and striatum (Rotge et al., 2010).

2.4.3. Effects of antiglutamatergic agents on OCD

Consistent with the evidence on increased glutamatergic function in OCD, initial reports indicate that agents with antiglutamatergic activity such as riluzole, which can decrease glutamate transmitter release (by inhibiting the selective persistent sodium inward current), may be useful in the treatment of obsessive–compulsive disorder (Bhattacharyya and Chakraborty, 2007; Coric et al., 2005; Grant et al., 2010; Pittenger et al., 2008, 2006). The evidence is preliminary, and includes evidence from other agents that affect glutamatergic function (Ting and Feng, 2008).

2.4.4. Possible ways in which the hyperglutamatergia acts

2.4.4.1. Overstability of attractor networks for action and motor function. One way in which the hyperglutamatergia may act is by increasing the stability of attractor networks in parts of the motor system high in the cortical hierarchy which by maintaining their activity hold a particular movement or movement sequence or action engaged.

2.4.4.2. Overstability of attractor networks for cognitive function leading to decreased cognitive flexibility. A similar increase in stability in the lateral prefrontal cortex cognitive system could maintain the short-term memory required for top-down attention (Deco and Rolls, 2005a; Rolls, 2008) in an overstable state, and make a person undistractible (Rolls et al., 2008c), and show reduced cognitive flexibility in switching from one rule or strategy to another (Deco and Rolls, 2003, 2005a, 2005c; Rolls, 2008).

2.4.4.3. Alterations in negative reward prediction error in the orbitofrontal and anterior cingulate cortex. There is a population of neurons in the orbitofrontal cortex that is involved in negative reward prediction error (Rolls, 2008, 2009b; Rolls and Grabenhorst, 2008). These neurons respond for example when an expected reward is not obtained when a visual discrimination task is reversed (Thorpe et al., 1983) (see Fig. 5), or when reward is no longer made available in a visual discrimination task (extinction) (Thorpe et al., 1983). These may be called "negative reward prediction error neurons". Different populations of such neurons respond to other types of non-reward, including the removal of a formerly approaching taste reward, and the termination of a taste reward in the extinction of ad lib licking for juice, or the substitution of juice reward by aversive tasting saline during ad lib licking (Rolls and Grabenhorst, 2008; Thorpe et al., 1983).

We tested the hypothesis that there are similar error neurons in the human orbitofrontal cortex, using a model of social learning. We found that orbitofrontal cortex activation occurred in a visual discrimination reversal task at the time when the face of one person no longer was associated with a smile, but became associated with an angry expression, indicating on such error trials that reversal of choice to the other individual's face should occur (Kringelbach and Rolls, 2003). We further tested the hypothesis that these neurons are necessary for behavior to change in humans when negative reward prediction error is received. We found that humans with damage to the orbitofrontal cortex are impaired at visual discrimination reversal for points or monetary reward, in that they continue to select the stimulus that was previously but is no longer rewarded (Hornak et al., 2004; Rolls, 1999b, 2005, 1994). This is what is predicted if these humans do not respond to negative reward prediction error. These findings have been confirmed (Fellows and Farah, 2003).

It is very notable that these negative reward prediction error neurons may continue firing for many seconds, sometimes until the start of the next trial, as illustrated in Fig. 5. This suggests that it is attractor short-term memory properties that maintain this error-related firing, which I propose is part of the way in which the error resets the rule neurons so that behavior then changes to follow another rule. For example, it is likely that there are rule neurons that maintain their activity while one rule is active (e.g. the triangle is rewarded and the square is punished) and that stop firing when another rule applies (e.g. the square is rewarded and the triangle is punished). The continuing firing of the negative reward prediction error neurons may be part of the mechanism by which the firing of the current rule attractor is quenched, so that the alternative attractor can become activated, with a possible mechanism analyzed by Deco and Rolls (2005c).

In relation to obsessive–compulsive disorders, I now consider the consequences of too much stability in both the negative reward prediction error attractor and in the rule attractor. One consequence would be that the error state would persist much longer than usual, and this might lead the human to make repeated attempts to correct the error (by for example repeatedly checking that the door is closed, or repeatedly washing the hands). Another consequence would be that the rule neurons, which enable behavior to flexibly switch from one rule to another when an error is received, would be overstable, so that a cognitive rule or set would be inflexible. These are I propose two particular ways in which overstability of attractor networks could contribute to the symptoms of obsessive–compulsive disorder.

In responding when the reward obtained is less than that expected, the orbitofrontal cortex negative reward prediction error neurons are working in a domain that is related to the sensory inputs being received (expected reward signaled by for example a visual stimulus, and the reward outcome provided by for example a taste stimulus). There are also error neurons in the anterior cingulate cortex that respond when errors are made (Niki and Watanabe, 1979), or when rewards are reduced (Shima and Tanji, 1998) (and in similar imaging studies, Bush et al., 2002). Some error neurons in the anterior cingulate cortex may reflect errors that arise when particular behavioral responses or actions are in error, and this type of error may

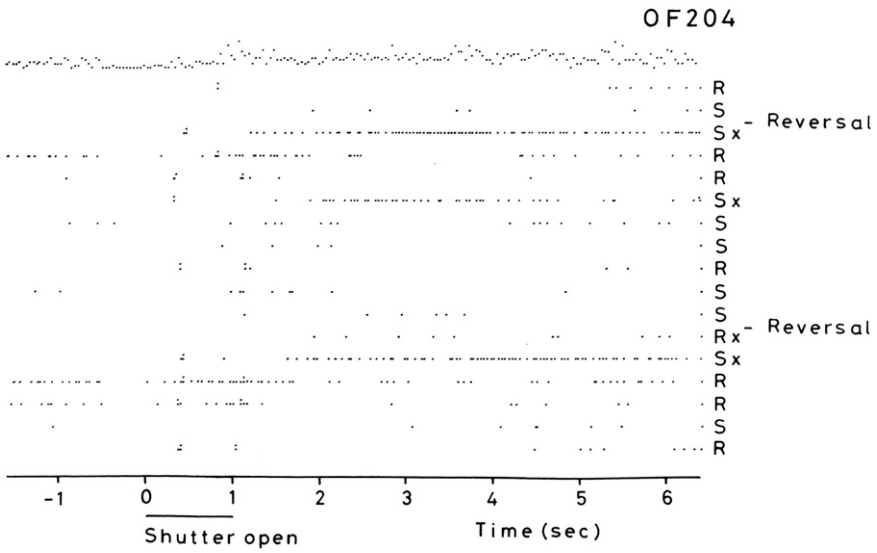

Fig. 5. Error neuron: Responses of an orbitofrontal cortex neuron that responded only when the monkey licked to a visual stimulus during reversal, expecting to obtain fruit juice reward, but actually obtaining the taste of aversive saline because it was the first trial of reversal. Each single dot represents an action potential; each vertically arranged double dot represents a lick response. The visual stimulus was shown at time 0 for 1 s. The neuron did not respond on most reward (R) or saline (S) trials, but did respond on the trials marked x, which were the first trials after a reversal of the visual discrimination on which the monkey licked to obtain reward, but actually obtained saline because the task had been reversed. (After Thorpe et al., 1983).

be important in helping an action system to correct itself (Matsumoto et al., 2007; Rudebeck et al., 2008; Rushworth and Behrens, 2008; Rushworth et al., 2004; Vogt, 2009), rather than, as in the orbitofrontal cortex, when a reward prediction system for stimuli needs to be corrected (Rolls, 2005, 2008). This anterior cingulate system could also contribute in an analogous way to persistence and inflexibility of actions.

This leads me to emphasize that the symptoms may be expressed differently in different patients with obsessive–compulsive disorder, depending on which particular cortical networks are most influenced by the overstability, with individual differences to be expected, given that Darwinian evolution is likely to be utilizing variation in parameters such as these to support evolution (Rolls, 2005). The argument is that genes define the goals for actions, i.e. the rewards and punishers, and that variation between the potency of different goals in different individuals is expected given that genetic variation and recombination are the driving forces of evolution (Rolls, 2005). This situation leads to differences in personality, in so far as personality can be defined in terms of sensitivity to different reinforcers (Eysenck and Eysenck, 1968; Gray, 1979; Rolls, 2005). In relation to obsessive-compulsive disorder, the particular emotional changes that are emphasized would therefore be expected to be somewhat different in different individuals, depending on where they lie in the multi-dimensional space defined by Rolls' goals (Table 2.1 in Rolls, 2005). In a sense, evolutionary mechanisms are exploring how to increase (genetic) fitness by producing different combinations of genes, in this case expressing the potency of different rewards and punishers, in different individuals (Rolls, 2005). This argument is extended here beyond emotions: individual differences in cognitive function are to be expected on the same principles of genetic variation for evolution. Overemphasis by hyperglutamatergia of the potency of different cognitive functions implemented in different cortical areas would therefore be expected to lead to diversity in the behavioral expression of the symptoms of obsessive–compulsive disorder. Thus a predominant pharmacological change, such as hyperglutamatergia, might lead to different cognitive and emotional changes in different individuals.

2.4.5. Implications for treatment

The theory about how the symptoms of obsessive–compulsive disorder could arise in relation to the increased stability of cortical attractor networks has implications for possible pharmaceutical approaches to treatment. One is that treatments that reduce glutamatergic activity, for example by decreasing glutamate transmitter release or by partially blocking NMDA receptors, might be useful.

Another is that increasing the inhibition in the cortical system, for example by increasing GABA receptor activated synaptic currents, might be useful, both by bringing the system from a state where it was locked into an attractor back to the normal level, and by making the spontaneous state more stable, so that it would be less likely to jump to an attractor state (which might represent a dominant idea or concern or action).

Part of the value of the theory is that it suggests that combinations of drugs each in low dose might together help to restore the stochastic dynamics to a useful working point. One such combination might be riluzole to reduce hyperglutamatergia, and an antianxiety drug such as a benzodiazepine to facilitate GABA. The aim would be to find a drug combination that is effective, and yet in which no one drug is present in such high concentration that it produces side effects.

However, I emphasize that the way in which the network effects we consider produce the symptoms in individual patients will be complex, and will depend on the way in which each person may deal cognitively with the effects. I also emphasize that over-correction of hyperglutamatergia could decrease attention and cognitive flexibility, producing symptoms like the cognitive symptoms of schizophrenia. Being aware of this possibility, and that the cognitive mechanisms of obsessive–compulsive disorder and of schizophrenia may be somewhat opposite, may be part of the value of this stochastic neurodynamics approach to both obsessive-compulsive disorder and schizophrenia (Rolls and Deco, 2010b). Careful titration of drug doses is indicated.

The theory also proposes that hyperglutamergia in the orbitofrontal cortex would tend to produce hyperemotionality, given that the positive and negative reinforcers that produce emotions are represented in the orbitofrontal cortex (Grabenhorst and Rolls, 2011; Rolls, 2005, 2008; Rolls and Grabenhorst, 2008).

I also emphasize that this is a stochastic neurodynamics theory of obsessive–compulsive disorder, that the theory must be considered in the light of empirical evidence yet to be obtained and may provide a foundation for medical advice but is not itself medical advice, and that

cognitive behavior therapy makes an important contribution to the treatment of such patients. I hope that the theory will stimulate further thinking and research in this area.

3. Schizophrenia

3.1. 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 and Seamans, 2008; Durstewitz et al., 1999, 2000a; 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, 2007b; Rolls, 2005, 2008; Rolls et al., 2008d). 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 approach, 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 modeled (Loh et al., 2007a; Rolls and Deco, 2010b). 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.

The stochastic dynamical systems approach that we utilize (Rolls and Deco, 2010b) is similar to that described above for OCD, but the exact effects in the system are quite different because we hypothesize that the transmitter changes are different. The full implementation of the equations for the neuron and synaptic dynamics and the results of the simulations of the system are described elsewhere (Loh et al., 2007a, 2007b; Rolls et al., 2008d), 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, 2010b).

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, 2010b). 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, 2010b; Rolls et al., 2008c, 2008d).

3.2. A neurodynamical hypothesis of schizophrenia

3.2.1. 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 more fully elsewhere (Amit, 1989; Hertz et al., 1991; Hopfield, 1982; Rolls, 2008; Rolls and Deco, 2002, 2010b).

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; Rolls et al., 2011; 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 states in attractor networks in the prefrontal cortex (Fig. 6). Specifically, NMDA receptor hypofunction, which has been associated with schizophrenia (Coyle, 2006; Coyle et al., 2010, 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 of the high firing-rate attractor states of the network (Loh et al., 2007a) (see Eq. (1)).

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 (see Eq. (1)). 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, 2010b). (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 (Rolls and Deco, 2010a)) 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 Eq. (1), and in *The Noisy Brain* (Rolls and Deco, 2010b). Thus, the stability of the attractor state is reduced. The result is difficulty in maintaining short-term memory and thus attention (see Fig. 6 and also (Durstewitz, 2007; Durstewitz and Seamans, 2002)). The shallower basins of attraction 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. Decreases in excitatory synaptic efficacy during late adolescence may be related to the onset of schizophrenia in those who are vulnerable (Rolls and Deco, 2010a).

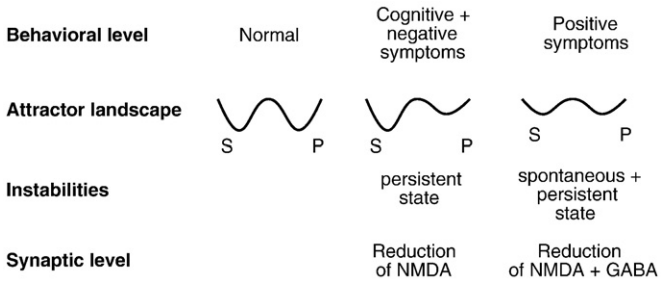

Fig. 6. Summary of the attractor hypothesis of schizophrenic symptoms and simulation results (see text). The first basin (from the left) in each energy landscape is the low firing rate spontaneous state (S), and the second basin is the persistent (or continuing) high firing rate attractor state (P). The horizontal axis of each landscape is the firing rate, increasing to the right. The vertical axis of each landscape is the energy potential. Modified from Loh et al. (2007a, 2007b).

3.2.2. 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 and colleagues 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 (Grabenhorst and Rolls, 2011; Paus, 2001; Rolls, 1999a, 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.

3.2.3. 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 Fig. 6). 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. 6. 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., 2008d). 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., 2008d) that treating schizophrenia patients with D2 antagonists could increase the GABA currents (Seamans et al., 2001a; 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 Fig. 6). 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., 2008d). 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 in the network and the spontaneous state (Fig. 7). 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. 6) (Loh et al., 2007a).

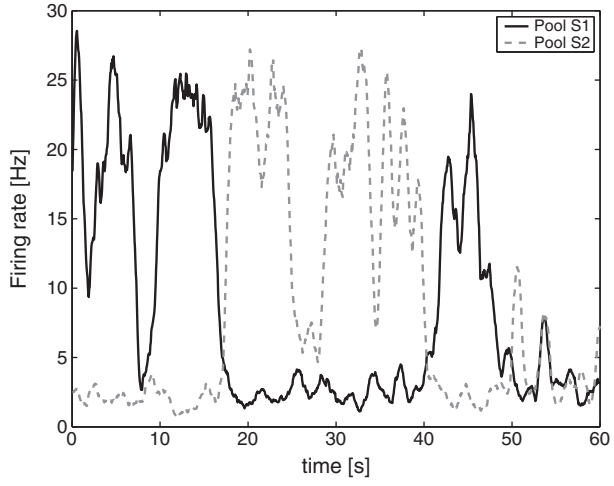

Fig. 7. Wandering between attractor states by virtue of statistical fluctuations caused by the randomness of the spiking activity. We simulated a single long trial (60 s) in the spontaneous test condition for reduced NMDA and reduced GABA synaptic efficacy (NMDA: −1, GABA: −1). The two curves show the activity of the two selective pools S1 and S2 over time smoothed with a 1 s sliding averaging window. The activity moves noisily between the attractor for the spontaneous state and the two high firing rate persistent attractor states S1 and S2.

3.3. 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, 2007b).

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, 2007b).

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., 2008d; Winterer et al., 2004, 2000).

The approach described here is different to an earlier computational approach in which spurious attractor states in attractor networks were related to some of the symptoms of schizophrenia (Hoffman, 1997; Hoffman and Dobscha, 1989; Hoffman and McGlashan, 2001), but it is now known that these spurious states are found with simplified neurons with binary firing rates (high or low) (Rolls et al., 2008d; Treves, 1991), rather than with the graded firing rate distributions of representations found in the brain (Rolls, 2008; Rolls and Deco, 2002; Rolls and Tovee, 1995).

3.4. Dopamine, glutamate, and stability

3.4.1. D1 receptor-mediated effects

A reduction in the ion-channel currents activated by (excitatory) NMDARs, and to some extent currents activated by inhibitory GABA receptors, could account for some of the different symptoms of schizophrenia, by diminishing the network stability, and thus increasing the variability of the network, which can be interpreted as a decrease in the signal-to-noise ratio (Brunel and Wang, 2001; Durstewitz, 2006; Durstewitz and Seamans, 2002; Durstewitz et al., 2000b; Loh et al., 2007a; Rolls, 2005, 2008; Rolls et al., 2008d; Wang, 2006). (For example, stability in such networks can be increased by dopamine-induced enhancements of the persistent Na^+ and N-methyl-D-aspartate (NMDA) conductances (Durstewitz et al., 2000a).) Alterations in dopamine (DA) modulation of these processes may —partly by influencing the NMDAR-activated currents (though DA has many effects (Durstewitz et al., 2000a; Rolls et al., 2008d; Seamans and Yang, 2004))—have an impact on the symptoms of schizophrenia, including those believed to be produced by effects on attractor networks that implement short-term memory and attention in the prefrontal cortex. Diminished prefrontal D1-receptor efficacy, by reducing the signal-to-noise ratio of neural network activity via lowering the NMDA currents, should diminish the stability of cortical

neuronal networks (Durstewitz, 2006; Loh et al., 2007a, 2007b; Seamans et al., 2001a; Seamans and Yang, 2004; Winterer, 2007; Winterer and Weinberger, 2004), and this could contribute to the cognitive symptoms.

Our simulations suggest that an increase in the NMDA component could improve the cognitive and negative symptoms of schizophrenia. In this context, the D1 receptor has been shown to modulate the performance of working memory tasks (Castner et al., 2000; Goldman-Rakic, 1999; Sawaguchi and Goldman-Rakic, 1991, 1994). An increase in D1 receptor activation has been shown to increase the NMDA current (Durstewitz and Seamans, 2002; Seamans and Yang, 2004), and modeling studies have shown that this increase is related to the stability of working memory states (Brunel and Wang, 2001; Durstewitz et al., 1999, 2000a). Imaging data also support the importance of the D1 receptor in schizophrenia (Okubo et al., 1997a, 1997b). We therefore suggest that an increased activation of D1 receptors might alleviate the cognitive and negative symptoms of schizophrenia (Goldman-Rakic et al., 2004; Miyamoto et al., 2005), by increasing NMDA receptor mediated synaptic currents. Atypical neuroleptics might use this mechanism by not only blocking D2 antagonists, but also by increasing the presynaptic release of dopamine which in turn would increase the activation of the extrasynaptic D1 receptors (Castner et al., 2000; Moller, 2005).

3.4.2. D2 receptor-mediated effects

Originally the dopamine hypothesis of schizophrenia focused on a hyperdopaminergic state in the striatum, which has a high density of D2 receptors (Stevens, 1973). D2 receptor antagonism remains a main target for antipsychotics (Coyle et al., 2010; Leuner and Muller, 2006; Seeman and Kapur, 2000). Dopamine receptor D2 antagonists mainly alleviate the positive symptoms of schizophrenia, whereas the cognitive and negative symptoms persist, especially for the typical neuroleptics (Mueser and McGurk, 2004). We found that the state corresponding to the positive symptoms can be reduced, leaving the cognitive/negative symptom still present, by changing the system from (NMDA:-1 GABA:-1) to (NMDA:-1 GABA:0). (The reduced GABA in the model of the positive symptoms had the effect of increasing the tendency of the system to leave spontaneous activity, and enter one of the attractors, which we related to intrusive thoughts and to hallucinations.) It has been found that D2 receptors decrease the efficacy of the GABA system (Seamans et al., 2001b; Seamans and Yang, 2004). (For example, Seamans et al. (2001b) found that the application of D2 antagonists prevented a decrease in eIPSC amplitude produced by dopamine.) Thus D2 antagonists would, in a hypersensitive D2 receptor state (Seeman, 2010), increase GABA inhibition in the network, and this we suggest could increase the stability of attractor networks involved in the positive symptoms of schizophrenia.

Seamans et al. (2001b) have suggested two distinct states of dopamine modulation. One is a D2-receptor-dominated state in which there is weak gating and information can easily affect network activity. The other is a D1-receptor-dominated state in which network activity is stable and maintained. The D2-receptor dominated state would correspond to schizophrenia, in which both NMDA and GABA currents are reduced (Seamans and Yang, 2004) such as proposed by our hypothesis. However, D2 antagonists are not able to restore the favorable balance between D1 and D2 receptor activation completely as they only alleviate the positive symptoms of schizophrenia. We suggest that the overall effect of D2 antagonists might be an enhancement in inhibition, which stabilizes the spontaneous state and reduces the aberrant activations in the network. In order to restore the working memory properties and a D1-receptor dominated state, the NMDA mediated currents must be enhanced, e.g. by applying D1 agonists. Excitation and inhibition are not merely antagonistic but implement different functions in the network dynamics.

3.5. Implications for the treatment of schizophrenia

The stochastic neurodynamics hypothesis suggests that treatments that increase the stability of the high firing rate attractor states of prefrontal cortex networks which implement cognitive functions (such as short-term memory and attention) by increasing the firing rates when in the high firing rate attractor state provide one approach to treating the symptoms of schizophrenia. Treatments that might produce this increase of firing rates include the glycine modulator of the NMDA receptor (Marek et al., 2010), metatrobic glutamate receptor agonists for e.g. mGlu5 which can facilitate NMDA receptor efficacy (Nicoletti et al., 2011), agents that increase AMPA functionality, agents that facilitate acetyl choline which will act to reduce synaptic adaptation and thus maintain high firing rate activity, and caffeine and nicotine as stimulants. The same treatments acting to increase the firing rates of neurons in the orbitofrontal cortex may reverse the negative, anhedonic, symptoms. An important concept is that although some of these interventions may not prove efficacious alone, they may when used in combination become efficacious, and at the same time minimize side effects that may be associated with individual interventions tried at high dose.

The hypothesis suggests that to treat the positive symptoms, treatments that increase GABA-mediated inhibition may also, simultaneously, be required. Such substances include the minor tranquilizers or antianxiety drugs such as benzodiazepine that act to facilitate the GABA-activated chloride channels. In this context, it is of considerable interest that this prediction of the model melds with clinical practice, in that schizophrenic patients are often treated with antianxiety drugs, in addition to other medications, though selective GABA agonists are likely to be more useful than benzodiazepines, which can have side effects (Coyle et al., 2010; Vinkers et al., 2010). Evidence that reduced GABA can increase psychotic symptoms in schizophrenia has been found (Ahn et al., 2011), and is consistent with the hypothesis. So is evidence from post-mortem studies that GABA system efficacy is reduced in schizophrenia (Gonzalez-Burgos et al., 2010). The altered GABA functionality may result inter alia in oscillations (Gonzalez-Burgos et al., 2010), and these may increase the stability of attractors by increasing the number of spikes exchanged between neurons (Deco and Rolls, in press; Smerieri et al., 2010).

The same approach suggests that agents that decrease GABA efficacy might lead to decreases in the stability of the spontaneous state of cortical networks when there is no input. The decrease of GABA functionality would lead to jumps to high firing rate states, and thus to a tendency to positive symptoms. It is noted that one such type of agent is the cannabinoids, which can decrease GABA efficacy (D'Souza et al., 2009). This provides a computational account of how the use of cannabinoids might tend to produce psychotic symptoms, and might trigger the vulnerable into schizophrenic-like states.

A recent clinical perspective on different pharmacological approaches to the treatment of schizophrenia is provided by Coyle et al. (2010).

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