# A computational neuroscience approach to schizophrenia: working memory and attentional deficits

ET Rolls, Ph.D., D.Sc.[1], G Deco, Ph.D.[2,3] and G Winterer, MD, Ph.D[4,5]

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[1]Oxford Centre for Computational Neuroscience, Oxford, UK. Edmund.Rolls@oxcns.org. URL: http://www.oxcns.org

[2]Computational Neuroscience, Universitat Pompeu Fabra, Barcelona, Spain

[3]Institució Catalana de Recerca i Estudis Avançats, Barcelona, Spain

[4] Cologne Center for Genomics, University of Cologne, Cologne, Germany. georg.winterer@uni-koeln.de

[5]Institute of Neurosciences and Medicine, Juelich Research Centre, Juelich, Germany

Correspondence to: Georg Winterer, Cologne Center for Genomics, University of Cologne, Cologne, Germany. georg.winterer@uni-koeln.de

We have recently described a computational neuroscience approach to understanding the symptoms and neural bases of schizophrenia [1-4]. In the stochastic neurodynamical approach, we consider the stability of neural systems in different cortical areas, and how different factors affect the stability in the face of the noise or randomness introduced into the system by the almost random spiking times of neurons for a given mean firing rate. We postulate that the cognitive symptoms, including impaired short-term memory especially in the presence of distracting events, which in turn impairs attention due to instability of the short-term memory systems that provide the source of the bias for top-down attentional control [5-8], are related to instability in attractor networks in the prefrontal cortex that implement short-term memory and control attention. The stability of the attractors is reduced by factors that reduce the firing rates of the neurons when they are in the high firing rate state that normally maintains the attractor-based short-term memory. The factors in schizophrenia that may produce these effects include reductions in the efficacy of cortical glutamate systems[9], of dopamine systems acting through the D1 receptors [3, 10], and a reduced synaptic spine density [4]. (The loss of excitatory synapses in the prefrontal cortex at adolescence is especially great in those diagnosed with schizophrenia, amounting to 60% [11-13]). We postulate that the negative symptoms including the reduced affect are produced by decreased firing rates (produced by similar mechanisms) in the orbitofrontal and anterior cingulate cortex [14], which are involved in emotion and motivation [14-16]. We postulate that the positive symptoms are related not only to instability of the high firing rate attractor states, but also to instability of the low firing rate spontaneous states, which even in the absence of input may jump into a high firing rate state which might represent a hallucination or intrusive thought when occurring in semantic and long-term memory systems in for example the temporal lobes [1, 3, 7, 17]. This instability of the low firing rate states we ascribe for example to the reduced inhibitory GABAergic functionality, especially of the cortical parvalbumin-containing neurons, in schizophrenia [9, 18, 19].

It is important that computational theories, and their predictions, should be tested. We therefore welcome a recent investigation of working memory representations in chronic patients with schizophrenia who were mostly treated with clozapine [20]. In line with what might be predicted from our computational approach, a reduced capacity (in terms of the number of items that could be correctly remembered) was found in a working memory task. We interpret this as less stable and more noisy attractors of the recurrent networks that implement short-term memory, making different attractors susceptible to interference, and thereby reducing the working memory capacity [7]. Although these investigators did not find a greater difference between performance at a 1 s and 4 s short-term memory interval for patients, we note that at both delays the schizophrenic patients were impaired relative to controls, and that the controls themselves did not show an effect of this change in the delay. Whether one obtains an effect of different delays does of course depend on a number of factors, such as the design of the task, the task difficulty, the duration of the delay, and, importantly, whether distracting stimuli are present, for attractor neural networks with reduced firing rates become more susceptible to distracting stimuli [1], and under these conditions especially short-term memory may be impaired. We therefore believe that future studies with distracting stimuli present would be of interest, and indeed note that the same research group have reported that, as predicted, schizophrenia patients fail to overcome distractors during a working memory task, showing a deficit of top-down attentional control [21]. In future studies we believe that it would also be useful to combine behavioral studies of this kind with signal to noise measures of brain function [22-25], and to select clinically homogenous patient groups or subjects who are unmedicated or subjects at risk for schizophrenia.

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