Rethinking Schizophrenia

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The "discoordination" hypothesis asserts that a common pathophysiology underlies the failures of cognitive function that are characteristic of mental inflexibility and failures of cognitive control as observed in a variety of clinical conditions, including schizophrenia. The hypothesis derives from the notion that neural computations and representations within and between networks of cells depend upon temporally coordinated neural activity. Consequently, cognitive impairment emerges when this coordination is sufficiently aberrant, despite relatively normal single cell properties. This neural discoordination is thought to derive from inappropriate excitatory and inhibitory synaptic transmission that interferes with the ability of neurons to temporally organize their electrical discharge to maintain and switch between separate streams of information flow through neuronal networks.

Using the psychotomimetic phencyclidine (PCP) in rodents, I will summarize our findings from investigating cognition and cognitive dysfunction as a *complex dynamical systems* problem operating at multiple levels of biological organization. I will focus on work that contrasts intact place cell discharge in hippocampus (single hippocampal cells thought to signal spatial knowledge) and the simultaneous sub-second discoordination of their temporal discharge microstructure. These and related studies motivate rethinking of how neural networks encode cognitive variables like environments. I will argue that the ongoing neural activity within hippocampus and related networks is fundamentally-internally organized onto low-dimensional activity manifolds, such that unreliably-tuned, spatially-untuned, and non-stationary single cell activity generates multistable population excitation-inhibition dynamics that are fit to external features of the world, adjusted by experience, and distorted in neuropsychiatric conditions with prominent cognitive control deficits.