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Title

Dynamic Causal Modeling of fMRI data reveals disordered frontal-hippocampal-striatal interactions during associative learning in schizophrenia patients

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Abstract

Background: Associative learning is an ideal cognitive domain in which to study schizophrenia-related pathophysiology, disordered activation, and functional disconnection. In a recent study, we applied GLM analyses to an fMRI paired associative learning paradigm, demonstrating increased activation within the fronto-hippocampal-striatal circuit and decreased modulation by the hippocampus of all regions except the basal ganglia (Wadehra et al, 2013). However, conventional approaches to fMRI data are inadequate in discovering disordered effective connectivity between brain sub-circuits. Here, we report an extended analysis of this group of subjects, using Dynamic Causal Modeling (DCM; Friston et al., 2003) to investigate frontal-striatal-hippocampal dysfunction. DCM permits evaluation of competing models of network architecture distinguished at a second stage using a Bayesian selection framework. Coupling estimates between regions provide evidence of effective connectivity (Friston, 2005) related to endogenous connections and the modulatory effects of a task on these connections.

Methods: fMRI (4.0T) was collected in SCZ (n=12) and controls (n=10; 18≤age≤35yrs). Because DCM relies on Bayesian model selection (BMS) to identify the most appropriate generative model for the data relative to neurobiologically-plausible competitors, 144 models were constructed by permuting connections between 6 brain regions. In addition to three primary regions, the supra-network included visual, inferior temporal, and parietal cortices. This set of 2,736 models (144 models x 19 subjects) was submitted to a second-level Random Effects Analyses for BMS. Inter-group inferences were based on Bayesian averages of estimated network coupling (Penny et al., 2010). All analyses were conducted in SPM8.

Results: BMS identified one winning model with an exceedance probability 60% greater than its closest competitor. In this model, patients evidenced inhibitory fronto-hippocampal coupling, but hyper-excitatory striatal-hippocampal coupling.

Conclusion: These results demonstrate that DCM is sensitive to identifying reduced fronto-hippocampal coupling and compensatory increases in fronto-striatal coupling during associative learning in schizophrenia. Impaired fronto-hippocampal-striatal function is a hallmark of schizophrenia-related pathophysiology. The application of DCM to *in vivo* fMRI data constitutes a substantive new advance in the application and ability of fMRI to identify the correlates of schizophrenia-related pathophysiology (Wadehra et al, 2012).