143. HYPOFRONTALITY AND WORKING MEMORY DYSFUNCTION IN SCHIZOPHRENIA

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Hypofrontality, indexed by reduced glucose metabolic rate or blood flow, is a common though not uniform finding in studies of schizophrenia. We studied patients with schizophrenia and matched normal controls using a procedure designed specifically to tap working memory, a function commonly attributed to the prefrontal cortex. Regional cerebral bloodflow (rCBF) was measured during performance of a nonspatial memory task, and compared to rCBF during a simple target detection task, which controlled for non-memory-related factors involved in performance. In normal subjects this procedure produces a reliable increase in rCBF in the dorsolateral prefrontal cortex bilaterally. Despite the fact that patients showed significant impairment on performance in the memory task (but not the control task), they did not show decreased prefrontal rCBF response. In fact, patients showed a tendency toward increased prefrontal rCBF; however, patients did fail to activate the right inferior temporal cortex and the precuneus, as compared to controls. Since the blood flow changes observed during cognitive activation studies are typically associated with presynaptic metabolic activity, our results may still be consistent with prefrontal dysfunction in schizophrenia. The activation observed in PFC may be due to intact afferents to this area, while PFC units themselves may fail to sustain this. This, in turn, could account for the failures of activation observed in other regions, such as inferior temporal cortex. If such an interpretation is correct, these results have significant implications for neuropathological hypotheses based upon changes in rCBF observed in functional brain imaging studies.

144. MODELING MEMORY-GUIDED TASKS IN SCHIZOPHRENIA

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We have used the asymmetric diffusion learning algorithm to model visually and memory-guided saccadic eye movements. A growing body of evidence from primate experiments indicates a role for frontal cortex in the maintenance of memory representations needed to support delayed responses. The system is clinically interesting because schizophrenic patients show deficits in memory-guided but not in visually guided eye movements. Specific neural modeling achievements include single- and multiple-hidden layer models of the oculomotor delayed-response and antisaccade task. These models produce qualitatively similar behavior to primate experiments, under both control conditions and putative catecholaminergic manipulations in the prefrontal cortex. In addition this modeling effort has led to a new understanding of how memory representations could be developed and sustained in the prefrontal cortex. The key result is the manner by which memory representations are chosen and maintained as the result of sequential input through circuits. Unlike earlier models requiring specific recurrent circuitry to create a population of "memory cells," in this model maintenance of memory representations is an emergent property from an interaction between the circuit architecture and the input dynamics.

145. VALIDITY STUDIES IN FUNCTIONAL MAGNETIC RESONANCE IMAGING: APPLICATION TO SCHIZOPHRENIA

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Functional magnetic resonance imaging (fMRI) is a new technique for investigating cognitive function. Before fulfilling its promise for longitudinal, noninvasive investigation in individual normal and schizophrenic subjects, several methodological questions must be addressed. How does one avoid false-positive results in the face of thousands of multiple comparisons, while still maintaining adequate power to detect small, task-related changes? Does activation remain stable over time? How does the pattern of brain activation seen in fMRI compare to that seen with other methods, such as PET? First, we present a method for identifying significant areas of neural activity, which improves power by 3–4-fold over standard approaches used in functional imaging without sacrificing false-positive protection. This is accomplished by using the size as well as the intensity of a putative activated region to distinguish true signal from noise. Second, we tested longitudinal reliability of fMRI activation maps using a series of test-retest studies of frontal cortical activation in normal subjects performing a working memory task. We found a voxel-wise correlation between studies ≥ 0.6 (n = 3 subjects; ∼10,000 voxels/subject). We also present one subject, studied in the same task in both PET and