14. Neuroimaging, Functional

ACTIVATION OF PREFRONAL CORTEX BY THE REPRESENTATION AND MAINTAINANCE OF CONTEXT INFORMATION

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We have suggested that a number of cognitive deficits in schizophrenia reflect a disturbance in the representation and maintenance of context, due to a prefrontal cortex (PFC) dysfunction. To test this hypothesis, we modified a version of the Continuous Performance Test (CPT-AX) by varying the delay over which individuals need to maintain context. A number of studies using this task have supported the behavioral predictions of our hypothesis. However, we have yet to directly test whether PFC supports context maintenance. We used fMRI to examine activation of PFC during performance of the CPT-AX in eleven healthy controls. To examine the time course of activation, we acquired multiple scans per trial. Activity was observed in dorsolateral PFC that was sensitive to delay length and sustained throughout the delay period. Moreover, the inclusions of conditions controlling for task difficulty revealed that PFC activity was unaffected by generalized increases in mental effort. In contrast, parietal cortex showed a time-varying delay-related response, and anterior cingulate activity increased with task difficulty. These results strongly support the hypothesis that the PFC is an important neural substrate underlying the representation and maintenance of context, and suggest that schizoprenic behavioral impairments in the CPT-AX may reflect a PFC dysfunction.

POSITRON EMISSION TOMOGRAPHY IN SCHIZOPHRENICS TREATED WITH ATYPICAL AND TYPICAL NEUROLEPTICS

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Previous studies with positron emission tomography (PET) and fluorodeoxyglucose (FDG) have indicated that an increase in striatal metabolic rate is observed following neuroleptic treatment. Treatment with clozapine showed less effect on the metabolic rate of the striatum and more change in the cortex than observed with haloperidol. Low striatal metabolic rates at baseline in unmedicated patients predicted subsequent improvement on haloperidol. In the current study a series of 16 patients are being entered into a randomized double-blind 6-week crossover study contrast of sertindole (a new antipsychotic medication with activity at $5HT_2$, D_2, D_3, and $alpha_1$ receptors) with haloperidol. PET scans (4.5 mm FWHM resolution) with FDG and a learning memory activation task chosen to activate frontal-temporal areas are obtained at the end of each 6-week period. High resolution SPGR magnetic resonance images at 1.2 mm spacing are obtained and coregistered to the PET scans. The basal ganglia are traced on the MRI and 3D metabolic images calculated and analyzed in 3D following morphing to the average contour of the group. A new method using coronal sections and thin-plate spline warping with 34 defined anatomical landmarks allows unique assessment of the nucleus accumbens and the ventral striatal area. The frontal and temporal lobes are analyzed with MRI-based tissue segmentation templates. Results in a companion cohort of not-previously presented, newly and identically scanned unmedicated and never-medicated patients ($n=18$) and age- and sex-matched controls ($n=25$) indicate confirmation of earlier reports of reduced metabolic rate in the striatum in schizophrenia. Pilot results in the current sample reveal a significant sertindole effect restricted to parts of the caudate nucleus and completely skipping the putamen and ventral striatal areas previously most strongly affected by haloperidol.

PROTON MAGNETIC RESONANCE SPECTROSCOPY AND ABERRANT NEURODEVELOPMENT: FRONTAL LOBE METABOLISM IN ADOLESCENT-ONSET SCHIZOPHRENIA AND IN AUTISM

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The ability of MR spectroscopy to provide in-vivo quantitative information on cerebral metabolism is helpful in clarifying the relative contributions of neurodevelopment versus neurodegeneration to the pathogenesis of schizophrenia. MRS studies of the frontal lobe in schizophrenia report (1) hypometabolism, suggestive of increased synthesis and breakdown of membrane phospholipids (2) reduced N-acetylaspartate, a putative neuronal marker, and (3) decrements in glutamate/glutamine. In relative contrast, the increased synthesis and breakdown of phospholipids in autism occurs against a hypermetabolic background. This proton MRS study provides a direct comparison of frontal lobe metabolism between schizophrenia and autism (an unequivocal neurodevelopmental disorder). The focus on adolescent-onset schizophrenia helps obviate the confound of illness chronicity and speculatively, may select a more neurodevelopmental form of the disorder.

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