Schizophrenia II
Thursday, May 11, 2:30 PM–5:00 PM
Location: Wrigley
Chair: David L. Braff

48. MEDIAL TEMPORAL LOBE MEMORY SYSTEM DYSFUNCTION IN RELATIVES OF PATIENTS WITH SCHIZOPHRENIA


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Growing evidence indicates that nonpsychotic relatives of patients with schizophrenia have subtle brain abnormalities in limbic, paralimbic and cortical regions. Verbal memory deficits in adult relatives have also been demonstrated. In this study we present more comprehensive morphometric analyses of the limbic and paralimbic cortices, to test the hypothesis that brain volume reductions, in a distributed memory encoding system, are associated with verbal memory deficits, and that they are more severe in nonpsychotic relatives with two schizophrenic family members (“multiplex”) as compared to one member with the illness (“simplex”). Subjects were 45 nonpsychotic first degree relatives of patients with schizophrenia and 48 matched normal controls. Sixty contiguous 3 millimeter coronal, T1-weighted 3D magnetic resonance images of the entire brain were acquired on a 1.5 Tesla magnet. Cortical and subcortical gray and white matter were segmented using a semi-automated intensity contour mapping algorithm. After segmenting the hippocampus and amygdala as a continuous volume, we parcellated the hippocampus from the amygdala. We used a new method to parcellate the fornix and mamillary bodies, along with the hippocampus, and the parahippocampal gyrus. Findings showed that the relatives had significant volumetric reductions in the left hippocampus, and parahippocampal gyrus bilaterally, and that these were more severe in the relatives from “multiplex” families. Verbal memory deficits were significantly associated with hippocampal and parahippocampal volumes in the direction of smaller volumes, worse memory performance. These new data on cognitive and brain endophenotypes provide clues to the pathophysiology of schizophrenia.

49. COGNITIVE DEFICS PREDICT PREFRONTAL VOLUME DECLINE IN SCHIZOPHRENIA

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Schizophrenia is associated with neurocognitive impairment and cortical gray matter volume deficits, particularly in prefrontal and temporal cortical regions. In an earlier longitudinal analysis, we examined MRI brain volume changes over an average interval of four years in 24 schizophrenic men (age = 39.4 ± 6.4 years) and 25 normal control men (age = 40.7 ± 8.9 years). Patients exhibited faster rates of cortical gray matter volume decline than controls, particularly in fronto-temporal regions, and greater symptom severity was associated with faster rates of volume decline among patients. In this report, we examined whether neurocognitive function assessed at Scan 1 predicted the rate of regional cortical gray matter loss over time in a subgroup of these subjects (patients n = 10 to 17, controls n = 20 to 22, depending on availability of cognitive measures). Neurocognitive composite scores derived from individual measures representing executive functions, declarative memory, short-term memory/fluency, visuospatial function, and upper limb motor function were correlated with MRI slopes (volume change/interscan interval) for six cortical gray matter regions in both groups. In patients, deficits in executive and memory functions, but not visuospatial or motor functions, selectively predicted the rate of volume decline in prefrontal gray matter; these relationships were not observed in the controls. Additional analyses based on individual neuropsychological measures showed that deficits in working memory, attention, psychomotor speed, fluency, and overall declarative memory predicted the rate of prefrontal gray matter decline in patients, but not controls. Thus, cognitive, but not motor, impairment in schizophrenia is associated with progressive volume loss in the prefrontal cortex.

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50. ZIPRASIDONE BLOCKS KETAMINE-INDUCED BRAIN METABOLIC ACTIVATION

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Subanesthetic doses of ketamine induce behavioral effects in healthy individuals that resemble positive, negative, and cognitive symptoms of schizophrenia. In stabilized schizophrenia patients, ketamine can induce psychotic symptoms that are remarkably similar to those experienced during active phases of their illness. Such findings have led to the hypothesis that decreased NMDA receptor function may be a predisposing or causative factor in schizophrenia. We previously found that clozapine and olanzapine, but not haloperidol or risperidone, blocked ketamine-induced brain metabolic activation, as measured by $^{14}$C-2-deoxyglucose (2-DG) uptake in rats (Biological Psychiatry 45 Abstract 180, 1999). The present study examined the effects of ziprasidone on ketamine-induced alterations in uptake. Ketamine (25 mg/kg) increased 2-DG uptake in specific brain regions, including limbic cortical regions, hippocampus, nucleus accumbens, basolateral amygdala, and anterior ventral thalamic nucleus. Pretreatment of rats with ziprasidone (5 mg/kg) blocked ketamine-induced changes in 2-DG uptake in all brain regions studied. The results demonstrate, in an animal model with potential relevance to schizophrenia, that ziprasidone produces effects similar to clozapine and olanzapine. The reduction of ketamine-induced brain metabolic activation by “atypical” antipsychotic drugs suggests that antagonism of the consequences of reduced NMDA receptor function could contribute to therapeutic mechanisms of these agents. The model of ketamine-induced alterations in 2-DG uptake may be useful for understanding the complex neural mechanisms of atypical antipsychotic drug action and may provide a means to discriminate full from partial atypical agents.

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