139. AUDITORY PROCESSING DURING SPEECH PRODUCTION IN SCHIZOPHRENIA

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Auditory hallucinations represent a cardinal and disabling symptom of schizophrenia; their pathophysiology remains elusive. The content and intensity of auditory hallucinations can correlate with subvocal speech. Normal subjects show automatic inhibition of auditory processing of self-generated speech during reading aloud, i.e., auditory cortices are equally active during reading aloud as during passive viewing of the same words. To determine whether patients with schizophrenia hallucinate because of a failure to suppress auditory processing of their own speech production, we measured, using PET, the cerebral blood flow in eight patients with schizophrenia (DSM-III-R) during two tasks of single-word processing: silent passive viewing vs. reading aloud of individual concrete nouns presented once every 3 seconds. Reading aloud, as compared to silent passive viewing, did not significantly increase activity in auditory cortices. The absence of activation of auditory cortices did not result from generalized deficit in enlisting brain regions relevant to task execution, because Broca's area was significantly recruited. Patients with schizophrenia, like normal controls, automatically suppress processing of their own speech. Therefore, auditory hallucinations in schizophrenia do not result from loss of self-inhibition between speech production and perception. (Supported by Scottish Rite Schizophrenia Research Fund, Matt Kaul Fund for Schizophrenia Research, and the Department of Veterans Affairs.)

140. WISCONSIN CARD SORTING IN THE YOUNG ADULT OFFSPRING OF SCHIZOPHRENICS

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As children of schizophrenics are at higher risk for developing illness than offspring of nonschizophrenic parents, studies can reveal much about genetic markers of schizophrenia. Cognitive deficits which are present in schizophrenic patients, their unaffected first-degree relatives, and offspring may be such markers. Abnormal performance on the Wisconsin Card Sorting Test (WCST) has been demonstrated in schizophrenics and their relatives; however, it has not been reported in their offspring. The present data were collected as part of the New York High Risk Project, a longitudinal study of attention, cognitive, and clinical functioning in the offspring of schizophrenics (HRs2), affective disorder (HRAff), and normal comparison (NC) parents. RDC diagnoses were established by semistructured interview using the SADS-L. Offspring with overt psychiatric illness were removed from these analyses. Groups were matched in age (n = 60 HRS2, mean age = 25.3 years, n = 58 HRAff, age = 25.5; n = 118 NC, age = 25.3). Dependent measures were perseverative errors and responses, total errors, number of categories achieved and failure to maintain set from the WCST, and pronted Full Scale IQ (FSIQ) estimated from selected WAIS-R subs tests. HRS2 subjects made significantly more WCST perseverations, total errors, and set failures compared to HRAff and NC subjects. WCST performance was unrelated to FSIQ in HRS2, but correlated with FSIQ in HRAff and NC subjects. These analyses suggest that WCST performance in offspring of schizophrenics is similar to that of schizophrenic patients and distinguishes HRS2 from children at risk for nonschizophrenic illness. Thus, WCST may be a specific cognitive marker of susceptibility to schizophrenia.

141. SCHIZOPHRENIC DEFICITS IN PROCESSING CONTEXT: A TEST OF NEURAL NETWORK SIMULATIONS

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Our previous work with computational modeling suggests that schizoprenic deficits in signal detection, attention, and language processing may all be related to a common disturbance in the ability to maintain contextual information over time, and use this to inhibit inappropriate responses. Here, we report a study that tested predictions made by these models. Patients with schizophrenia were tested in a new variant of the continuous performance test (CPT), designed specifically to elicit deficits in the processing of context information. Patients in a first episode of illness were studied, as well as patients later in the course of illness, both on and off neuroleptic medication. Unmedicated patients showed a selective deficit in a task condition that probed the ability to maintain context information over time, and use this information to inhibit a pre-potent but incorrect response. This deficit correlated strongly with positive symptoms and was modified by neuroleptics. The observed pattern of deficits was predicted by our models, and provides support for a theory concerning the role of dopamine in prefrontal cortex function and its impairment in schizophrenia. Furthermore, our results indicate that such deficits may worsen over the course of illness, as suggested by a Kraepelien view of schizophrenia.

142. LEXICAL PRIMING IN SCHIZOPHRENIA: THE EFFECTS OF ANTI-Psychotic MEDICATION

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We examined lexical priming in 75 medicated and 25 unmedicated DSM-III-R schizophrenics, 10 depressed controls, and 28 normal controls. Our sample population and experimental design were chosen to address mediation and methodological issues related to lexical priming and the assessment of automatic components of processing in schizophrenia. Word naming was used instead of lexical decision to provide more precise measures of automatic processing, given the status of this construct in previous theorizing about schizophrenic language deficits. We used five SOAs to systematically examine the time course of priming among schizophrenics. Our results indicated that at shorter SOAs (200, 300 msec), medicated schizophrenics displayed enhanced priming compared to other groups, while priming among unmedicated schizophrenics was similar to normal and depressed controls. At longer SOAs (700, 900 msec) unmedicated schizophrenics did not display significant priming effects, while normal and depressed controls did. Medication dosage in chlorpromazine equivalents was positively correlated with priming at all SOAs other than 950 msec. These results suggest that previous reports of enhanced priming in samples of medicated schizophrenic subjects may have been influenced by the effects of antipsychotic medications. The normal priming displayed by unmedicated schizophrenics at the shorter SOAs suggests that automatic components of priming operate normally in unmedicated schizophrenics. In conjunction with the lack of significant priming effects at the longer SOAs among unmedicated schizophrenics, these results suggest that it may be more relevant to focus on disturbances in strategic or higher-level components of language processing in schizophrenia.

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 prefrontal 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 respond. This, in turn, could account for the failures of activation observed in other regions, such as inferior prefrontal 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 tasks. 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 hypothesis: that 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