367. IMAGING MEMORY SYSTEMS IN THE NORMAL HUMAN BRAIN

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Since the introduction of x-ray computed tomography (CT), now nearly 25 years ago, we have seen the rapid development of other new technologies for the safe and remarkably detailed imaging of the function as well as the anatomy of the normal human brain. These have included positron emission tomography (PET) and, more recently, functional magnetic resonance imaging (fMRI). In parallel, more sophisticated electrical recording techniques such as event related potentials (ERP's) and the newer magneto encephalography (MEG) have received considerable attention. Together these new techniques now provide a formidable array of tools to explore learning and memory systems in the normal human brain, an area previously unexplored. Studies of learning and memory have accounted for a surprisingly large fraction of the research done to date with PET and fMRI. This is attested to by several recent comprehensive reviews (see Buckner and Tulving, *Handbook of Neuropsychology* 10:439–466,1995; Ungerleider, *Science* 270:769–775,1995). The very distributed nature of cortical systems supporting memory functions has become evident. Distinctions between encoding and recall in terms of the neural systems supporting them have emerged. Rapid reorganization or cortical systems has been observed as a consequence of learning. The first look at the neurobiological substrate for priming has occurred. Overall, these new technologies coupled with sophisticated psychological paradigms have expanded our vision of learning and memory in the normal human brain from a more traditional, hippocampocentric view. Our understanding of the cognitive aspects of mental illness are likely to be major beneficiaries of this work.

368. NEURAL SYSTEMS UNDERLYING LEARNING AND MEMORY

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The retrieval of factual knowledge does not depend on a single brain system but rather on several, partially segregated, neural systems. The experimental neuropsychological investigation of large numbers of patients with focal lesions of the telencephalon, reveal that knowledge concerning concrete entities and actions depends on distinct neural components located in higher-order association cortices. Based on 3-D MR reconstruction techniques (BRAINVOX; MAP-3), we have identified the components critically related to knowledge for unique and nonunique entities are located largely in occipitotemporal regions, while those concerning actions are located largely in prefrontal/premotor and parietal regions. Data from functional imaging studies (using PET and fMR), from our laboratory as well as others, reveal compatible evidence. The components we have uncovered are not rigid centers. Rather they are dynamic, individualized, and modifiable regions which hold dispositions on the basis of which representations describing aspects of varied concepts can be transiently reconstructed in early sensory cortices.

369. SELECTIVE PHARMACOLOGICAL LIMBIC ACTIVATION: PHENOMENOLOGY AND BLOOD-FLOW

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Limbic and paralimbic structures are essential to the subjective, autonomic and endocrine aspects of emotions. However, the specific contribution of different human limbic structures have not been identified. Using procaine hydrochloride injections, we observed robust and very selective PET activation of limbic and paralimbic structures in healthy volunteers (bilateral anterior cingulate cortex, insular cortex and amygdala/parahippocampal regions). This brain activation was accompanied by powerful and varied emotional responses – including panic anxiety, sadness and euphoria. Subjective experiences elicited by procaine differed both between and within subjects (across successive injections). Between-subject variance was related to previous experience with recreational drugs. Drug-naive subjects were more likely to experience anxiety whereas drug-exposed subjects were more likely to experience euphoria. In a subsequent study we controlled within-subject variance experimentally by inducing positive, negative and neutral mood states just prior to injections of procaine or placebo. Procaine potentiated mood experiences. In combination with PET, this factorial design can identify patterns of brain activation associated with the different subjective, cardiovascular and endocrine responses of subjects across mood state and drug condition. It can also disentangle mood state from other physiological effects of procaine. We will report the results of this on-going study.

370. CONTEXT PROCESSING DISTURBANCES IN SCHIZOPHRENIA: EMPIRICAL TEST OF A THEORETICAL MODEL

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Despite a large body of research, relatively little progress has been made in understanding schizophrenic cognitive deficits, or their neurobiological basis. In part, this may be due to the need for a more theoretically-driven approach to understanding such deficits. In previous work, we constructed neural network models of performance in a set of cognitive tasks in which schizophrenics are known to exhibit deficits. This work resulted in a specific hypothesis concerning a function of prefrontal cortex (PFC), and its involvement in schizophrenia: that PFC is responsible for the processing of context, and that a disturbance in this mechanism is responsible for a number of cognitive deficits observed in schizophrenia. These models made theoretical predictions regarding task dimensions that should be relevant to performance deficits in schizophrenic patients. Specifically, they predicted that schizophrenics would

show the greatest deficits in the conditions requiring that context be maintained over a delay, particularly when it must be used to elicit a context-mediated response in favor of a competing dominant response. To test these predictions, we modified three tasks - the AX-CPT, the Stroop task, and a lexical disambiguation task - and administered them to inpatient and outpatient schizophrenics, as well as patients with major depression and non-psychiatric controls. The results corroborated our predictions concerning schizophrenic performance in context-sensitive conditions of these tasks, and correlations of performance in these conditions across tasks. These findings provide strong support for our hypothesis concerning a specific disturbance in the processing of context in schizophrenia.

371. MAGNETIC RESONANCE SPECTROSCOPIC INESTIGATIONS OF AFFECTIVE DISORDERS

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Magnetic resonance spectroscopy (MRS) is a non-invasive tool for *in vivo* chemical analysis. We have been studying brain metabolism in patients with affective disorders using ^{31}P-MRS and ^{1}H-MRS. The results of these studies are summarized as follows: (1) Phosphomonoester (PME) peak was elevated in manic patients with bipolar disorder (12.3±1.9%, n=17). PME was lower in the euthymic state (10.2±1.5%, n=17) than that in normal controls (11.4±1.6%, n=17). (2) Phosphocreatine (PCr) was lower in the left frontal lobe in bipolar depression (8.4±1.0%, n=11) compared with normal controls (9.8±1.1%, n=21). Decrease of PCr correlated with higher scores of Hamilton Depression Rating Scale (r= -0.75). PCr in the frontal lobes was low in all psychiatric states in patients with bipolar II disorder. (3) Intracellular pH was lower in euthymic patients with bipolar disorder treated with lithium (7.01±0.04, n=40) than normal controls (7.05±0.04, n=60), while it did not differ from controls in manic or depressive states. (4) The choline containing compounds (Cho) measured by ^{1}H-MRS was increased in both bipolar and unipolar depression in the basal ganglia. Decrease of PCr is of particular interest because PCr was increased in the left frontal lobe in schizophrenia. This may provide a clue to clarify the biochemical difference in bipolar disorder and schizophrenia. Alteration of intracellular pH is also of interest because it may relate to clinical action of lithium. These findings will provide new research strategies to study the neurochemical basis of bipolar disorder.

372. ^{1}H MRS INVESTIGATION OF PANIC DISORDER

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There is increasing evidence to suggest the involvement of brain mechanism(s) in the etiology of pathological anxiety, particularly panic disorder. However, older generation brain imaging techniques, capable of assessing brain anatomical structure, have not identified consistent structural abnormalities. In this regards, the development of modern functional imaging techniques, such as, magnetic resonance spectroscopy (MRS) are beginning to elucidate underlying brain physiologic abnormalities which may be responsible for panic disorder. We have undertaken a series of studies of panic disorder using ^{1}H MRS to investigate brain metabolic responses to acute panic precipitated by chemical challenges, such as intravenous sodium lactate infusion or during controlled hyperventilation. Single voxel findings from the insular cortex region indicate excess brain lactate rise among panic subjects during panic precipitated by lactate infusion and continued rises post-infusion in relationship to decreasing blood lactate levels. Similarly, during vigorous hyperventilation controlled by capnometry, asymptomatic panic subjects demonstrated significantly greater brain lactate rises in comparison to matched controls. In total, findings suggest brain metabolic abnormalities which may help to explain theories of "suffocation false alarm" (Klein, 1993) postulated to be responsible for sudden, overwhelming panic. In addition, preliminary findings using proton echo-planar spectroscopic imaging (PEPSI) to map out the underlying neuroanatomical substrate in relationship to changing metabolic conditions during the precipitation of panic will be presented. These studies provide a model for unraveling underlying brain pathophysiological processes responsible for the production of panic. Work supported by NIMH (R01-MH50579).

373. PROTON MRS OF HUMAN BASAL GANGLIA DURING ACUTE COCAINE ADMINISTRATION

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Proton magnetic resonance spectroscopy (1H MRS) was used to evaluate changes in basal ganglia chemistry occurring in response to intravenous cocaine administration. Twenty-seven healthy and neurologically normal males, aged 28±5 years (mean±SD), provided informed consent to participate in the study. Subjects reported a history of casual cocaine use (13±14 lifetime exposures) and tested negative for the presence of drugs/alcohol immediately prior to the study. All studies were performed using a 1.5T clinical MR scanner. PRESS localization was used to acquire 1H MRS signals from an 8 cm^3 cubic volume surrounding the basal ganglia. Unsuppressed water spectra and water suppressed spectra containing resonances for N-acetyl-aspartate (NAA), creatine+phosphocreatine (Cr), cytosolic choline-containing compounds (Cho), and myo-inositol (Inos), were obtained at 5 min intervals at baseline and following the intravenous infusion (slow push over one minute) of placebo (n=7), 0.2 mg/kg cocaine (n=10) or 0.4 mg/kg (n=10). Following cocaine administration, the signal intensities of all intracellular resonances were increased in a dose-dependent manner. For the subjects receiving placebo, the mean intensities (±SD) of the resonance lines thirty minutes after injection, expressed as percent of the baseline value were, NAA (99±8), Cho (97±8), Cr (106±21), Inos (100±22), and water (100±2). Thirty minutes following the injection of 0.40 mg/kg cocaine, corresponding values were NAA (117±28) Cho (135±51), Cr (112±24), Inos (128±23), and water (100±2). The increases in the intracellular metabolite (NAA, Cho, Cr, and Inos) resonance intensities were all statistically significant. In contrast, the intensity of the water line remained constant, suggesting that cocaine