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 (ERPs) and the newer magnetoencephalography (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, hippocampal-centric view. Our understanding of the cognitive aspects of mental illness is 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 in 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, autonomc 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 schizophrenia 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 INVESTIGATIONS
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 31P-MRS and 1H-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±1.9%,
n=17) than that in normal controls (11.4±1.6%, n=17). (2) Phospho-
creatine (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=-.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 1H-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 intracellu-
lar 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. 1H 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 abnor-
malities which may be responsible for panic disorder. We have under-
taken a series of studies of panic disorder using 1H 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
relation 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 pro-
duction 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 cm³ 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
was not detected.