Results: Both tasks activated largely overlapping cortical networks typically engaged by verbal WM (i.e., bilateral dorsolateral PFC, Broca's area, parietal cortex). Increased WM load was associated with monotonically increased activity, and RI with greater and more enduring activity. Focal group differences on each task emerged in an overlapping region of the right dorsolateral PFC ($ps<.0001$): SZs showed lesser-magnitude activity increases under conditions of high WM and RI demands. Behaviorally, SZs performed more poorly than controls on measures of WM and RI, but not under control conditions.

Conclusions: Results demonstrate that SZs exhibit PFC-mediated deficits in WM *and* in over-riding prepotent response tendencies. Findings are consistent with the operation of a single underlying PFC-mediated cognitive control mechanism, and with physiological dysfunction of the dorsolateral PFC in schizophrenia patients.

308. COMT VAL$^{108/158}$MET POLYMORPHISM EFFECTS DLPFC EFFICIENCY IN HEALTHY INDIVIDUALS

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Background: The Val$^{108/158}$Met polymorphism in the catechol-O-methyltransferase (COMT) gene appears to predict the efficiency of dorsolateral prefrontal cortical (DLPFC) neuronal function as measured by BOLD fMRI. We sought to replicate this finding using the same behavioral protocol in a new cohort of healthy volunteers (HV) at 3 Tesla.

Methods: We studied 28 HV (10 females, 18males; mean age=36; matched for handedness and IQ) using the N-back WM task at 3T (GE-EPI RT) using a block design alternating between zero back and two back. The functional images were analyzed within SPM99 (Wellcome Department of Cognitive Neurology, FIL, UK). Because there have been prior demonstrations of a significant relationship between DLPFC activation and age, we covaried for age in all second level analyses.

Results: Neither WM accuracy (% correct) nor reaction time (RT) differed significantly between the three genotype groups (Val/Val, Val/Met, or Met/Met). At the group map level, there was an apparent allelic load effect wherein the COMT Val allele predicted the least efficient BOLD fMRI response in DLPFC (Area 9).

Conclusions: These fMRI data confirm prior results with a larger, independent cohort of healthy individuals. Combined with previous work, these new data suggest that allelic variation in COMT confers increased susceptibility to schizophrenia due to its affects on DLPFC neuronal function.

309. WORKING MEMORY AND PREFRONTAL CORTEX FUNCTION IN SCHIZOPHRENIA: REGIONAL AND MEMORY DOMAIN SPECIFICITY AND NON-SPECIFICITY

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Background: The schizophrenia literature has demonstrated relationships between impairments in working memory and prefrontal cortex (PFC) activity. Two issues arise when considering the functional significance of these findings. One issue is whether these impairments are regionally specific. A second issue is whether PFC impairments in schizophrenia are selective to working memory, or instead contribute to deficits in other domains (i.e., episodic memory). The current study examined these issues using fMRI to assess cortical function during performance of both working and episodic memory in patients with schizophrenia.

Methods: Participants were 38 medicated patients with DSM-IV schizophrenia and 48 healthy controls. All subjects were scanned with fMRI while performing three tasks, each with both verbal and non-verbal materials: 1) 2-Back version of the "N-back" (working memory); 2) episodic memory encoding; and 3) yes/no recognition.

Results: Patients with schizophrenia demonstrated impaired behavioral performance on both the working memory and episodic memory tasks, which were strongly correlated. Patients with schizophrenia demonstrated intact task-related activation of inferior/posterior PFC (BA 44/6/45), but impaired activation of more anterior/superior regions (BA 46/9). In addition, the same region of right dorsolateral PFC (BA 46/9) demonstrated impaired activation in patients during performance of both working and episodic memory tasks, while left dorsolateral PFC activity was impaired only during working memory.

Conclusions: The results indicated evidence for regional specificity of impaired PFC activation in schizophrenia, with more anterior/superior regions of PFC more impaired than inferior/posterior regions. In addition, the results suggest that right dorsolateral PFC may support cognitive processes important in multiple memory domains, rather than working memory specific processes. In contrast, abnormalities in left dorsolateral PFC activity were working memory specific, consistent with their hypothesized PFC for the maintenance of contextual information across time. Taken together, these results suggest that cognitive and PFC functional abnormalities need to be conceptualized in a framework broader than just working memory.

PAPER SESSIONS
Depression/Imaging
Friday, May 17, 2:30 PM-5:00 PM
Location: Flower
Chair: Mary L. Phillips

310. ENHANCED VISUAL CORTICAL RESPONSES TO FACIAL EXPRESSIONS OF SADNESS IN PATIENTS WITH MAJOR DEPRESSION

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Background: Identification of danger, e.g. fear and disgust, and reward, e.g. happiness, is vital for survival. Identification of distress, e.g. sadness, may be less critical: previous findings indicate an attentional bias towards sad expressions in depressed but not healthy subjects, and increased visual cortical activation to emotional but not sad expressions in healthy subjects.

Methods: In each of four 6-minute event-related fMRI experiments, right-handed healthy (n=9) and depressed (n=9) subjects viewed 10 facial identities expressing neutral, 50% (mild) and 100% (severe) intensities of one emotion (sadness, happiness, disgust or fear), each for 2s. Subjects viewed a fixation cross during the ISI (varied from 3 to 8s according to a Poisson distribution, average 4.9s). We employed orthogonal polynomial trend analysis to determine linear trends in activation to

neutral, mild, and severe facial expression intensity. These were then compared with analyses of variance.

Results: Visual cortical activation was demonstrated by all subjects to both intensities of all emotional compared to neutral expressions, and fixation cross. A linear trend was demonstrated in visual cortical activation to changes from neutral to 50% to 100% of all facial emotions, but significantly more ($p=0.05$) to fear, disgust and happiness than to sadness in healthy but not depressed subjects, and to sadness significantly more in depressed than in healthy subjects ($p=0.05$).

Conclusions: We report the first demonstration of a differential modulation of visual cortical activation by signals of danger/reward and distress in healthy but not depressed subjects, and a visual response bias to sadness in depressed patients.

311. ALTERED SEROTONIN 1A BINDING IN MAJOR DEPRESSION: A [11C]WAY100635 PET STUDY

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Background: Two studies have demonstrated lower 5-HT1A binding in depressed subjects using [11C]WAY100635 PET. Quantification of binding was based on the specific to nonspecific equilibrium partition coefficient (V3" = k3/k4) derived using the simplified reference tissue model (SRTM). This method uses the cerebellum as the input function and also introduces a significant bias when compared to full quantification with a three compartment kinetic model, shown to be the method of choice for this ligand in humans (Parsey et al. 2000). We therefore studied depressed patients with [11C]WAY100635 PET and an arterial input function to avoid these methodological problems.

Methods: 25 heatlhy volunteers and 24 subjects who met DSM-IV criteria for a major depressive episode (off of all psychotropic medications) were scanned in an ECAT EXACT HR+ camera for 110 minutes. All subjects had metabolite corrected arterial input functions. Regions of interest (ROIs) were drawn on individual MRIs except for the raphe ROI which was a fixed volume placed on each individuals mean PET scan. Time activity curves were generated from MRI coregistered PET images.

Results: No significant differences were detected between the healthy volunteers and patients in age (40.3 ± 15.3 vs. 40.2 ± 11.4), % female (48% vs. 58%), injected mass (8.2 ± 5.1 nmole vs. 7.1 ± 3.6 nmole), or clearance of the compound (141 ± 38 L/hr vs. 155 ± 29 L/hr). Lower 5-HT1A binding was found in the depressed patients. This was demonstrated by principal component analysis. 74% of the cumulative variance in the ROI binding potential is explained by the first principal component, 88% by the first and second, and 94% by the first three components combined. MANOVA on the first three principal components with sex and the inverse of the free fraction as covariates, shows a significant diagnosis effect ($p=0.045$). Post-hoc analysis reveals significantly lower binding in the cingulate cortex, amygdala, raphe nuclei, hippocampus, medial and orbital prefrontal cortex.

Conclusions: We have demonstrated lower 5-HT1A binding potential in depressed subjects using [11C]WAY100635 when accounting for sex and free fraction of the tracer. Future studies need to determine the reason for lower 5-HT1A binding and the effect of antidepressant treatment.

312. ABNORMALITIES IN MU OPIOID RECEPTOR BINDING AND ENDOGENOUS OPIOID RELEASE IN MAJOR DEPRESSION: CLINICAL AND NEUROENDOCRINE CORRELATES

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Background: One of the most frequently replicated findings in the Major Depression (MDE) literature is the dysfunction of stress-related responses, typically evidenced by increases in limbic-hypothalamic-pituitary-adrenal (LHPA) function. The endogenous opioid system and μ-opioid receptors is one of the neurotransmitter systems involved in responses to stress, as well as in the action of opiates and various substances of abuse. In the present study we examined whether the endogenous opioid system, through interactions with mu opioid receptors, is abnormally regulated in MDE, and the possible implications of this phenomenon.

Methods: Fourteen women diagnosed with moderate to severe MDE (SCID-IV, HDRS scores >20) and 14 matched healthy women were studied with PET and the selective mu receptor radiotracer [C-11]carfentanil. Subjects were studied under two conditions, a self-induced sustained sadness state and a neutral state, counterbalanced in order. Binding measures (Bmax/Kd) were obtained on a voxel-by-voxel basis using Logan plots and occipital cortex as reference region. T1-weighted MRI and PET images were coregistered and warped to sterotactic atlas coordinates. Statistical parametric maps of differences in receptor availability were then calculated between conditions and groups with SPM'99. Affect states were rated with the Positive and Negative Affect Scale (PANAS).