Subjects are scanned twice: after placement of nicotine patches and after placement of placebo patches. Order of nicotine/placebo patch administration is random and double blind. During scanning, subjects perform an auditory n-back task with two levels of verbal working memory load and two levels of selective attention load. To date, 10 smokers with schizophrenia and 10 smokers with no psychiatric illness have been studied. Subjects with and without schizophrenia did not differ in age, level of education, estimated IQ, reading achievement, numbers of cigarettes smoked per day, or total smoking exposure (pack-years). fMRI data show a significant interaction between diagnosis, patch condition, and working memory load. Relative to nicotine withdrawal, the presence of nicotine in plasma (active patch condition) is associated with enhanced activation of anterior cortical regions and putamen/insula under high verbal working memory load in smokers with schizophrenia. Smokers with no psychiatric illness do not show this effect. Supported by the Veterans Administration and by NIH grant M01RR00125

AN FMRI PARADIGM TO STUDY RESPONSES TO AVERSIVE STIMULI - A CENTRAL ROLE FOR LIMBIC STRIATUM

J. Jensen,* A. R. McIntosh, A. P. Crawley, D. J. Mikulis, G. Remington, S. Kapur
PET Centre, Centre for Addiction and Mental Health, Toronto, ON, Canada

The limbic striatum (ventral striatum in humans, the nucleus accumbens in rats) is critically involved in mediating the motivational salience of appetitive and aversive stimuli. It has been suggested that abnormalities in this system are critical to several neuropsychiatric disorders, most notably, schizophrenia and drug abuse. Several preclinical models have been developed to assess this system, conditioned approach and avoidance among them. The purpose of this study was to develop an fMRI paradigm, analogous to the preclinical models, to examine whether the ventral striatum plays a similarly important role in human motivational salience. Eleven subjects went through a paradigm based on aversive conditioning in an event-related fMRI experiment. As unconditioned stimulus (US) we used aversive electrical stimulations to the index finger where the intensity was titrated to when it was unpleasant but tolerable. Two colored circles were used as neutral stimuli. One (CS+) was paired with the US in 1/3 of the trials while the other colored circle (CS-) was never paired. Twenty-eight slices covering the whole brain were acquired in the axial plane with a GE 1.5 T scanner (TR=2.3s; TE=40ms). Data were realigned, normalized, spatially smoothed and temporally filtered. The main comparison of interest was 30 CS+ trials (in which no electrical stimulation was finally delivered, i.e. 2/3 of CS+ trials) to 30 CS- trials using a random effects analysis in SPM. The analysis showed the CS+ stimuli, even when not accompanied by electrical stimulations on every trial, caused robust activations in five clusters in limbic/paralimbic regions. The regions activated were bilateral anterior insula regions, bilateral ventral striatum and the anterior cingulate/medial frontal region. These findings fit with current theories that suggest a crucial role for the ventral striatum in conditioned motivational salience. This finding is also consistent with several animal models, most notably conditioned avoidance response (CAR), which also critically depends on ventral striatal functioning. Since CAR has a central role in preclinical testing of antipsychotics, we are now exploring whether this fMRI paradigm may serve a similar purpose in human studies.

FUNCTIONAL NEUROANATOMY OF AUDITORY SENSORY MEMORY

P. Johnston,* U. Schall, J. Todd, A. Dittmann-Balcar, M. Jupner, P. Ward, P. Michie
School of Medical Practice and Population Health, University of Newcastle, Callaghan, NSW, Australia

One of the most consistent findings over the past decade in schizophrenia research is a reduction in the amplitude of an early auditory event-related brain potential known as mismatch negativity (MMN). The current study is part of a series of experiments aiming to elucidate the underlying mechanism of MMN reduction in schizophrenia. By means of two functional brain imaging techniques we examined 6 healthy subjects using 15O PET and 10 healthy subjects using fMRI. We measured rCBF (PET) and BOLD contrasts (fMRI) derived from the comparison of blocks of stimuli either presented as a series of standard tones alone versus blocks of rare deviant tones that were interspersed among a series of standard tones (mismatch condition) while subjects were performing a visual distraction task (PET) or were watching a silent movie (fMRI). In addition, attention effects on mismatch processing were assessed in our PET study while possible confounding effects due to scanner noise was assessed by a no tone condition in the fMRI experiment. fMRI data were also analysed by employing an event-related haemodynamic response model. In line with previous EEG source modelling studies, we found temporal lobe and prefrontal cortical activation that was associated with auditory mismatch processing. (Supported by NH&MRC Neuroimaging Consortium, Neuroscience Institute for Schizophrenia and Allied Disorders, (NISAD), University of Western Australia, Small Research Grant, and University of Essen).

EFFECTS OF QUETIAPINE IN FIRST EPISODE SCHIZOPHRENIA. COMPARISON WITH DRUG NAIVE PATIENTS AND HEALTHY CONTROLS

H. M. Jones,* M. J. Brammer, R. Ohlsen, M. O'Toole, T. Taylor, R. Brown, S. V. Williams, L. S. Pilowsky
Ward DB2, Maudsley Hospital, London, United Kingdom

Introduction We present data suggesting that treatment with the antipsychotic quetiapine in first episode schizophrenia results in an improvement in frontal cortex function. Method Seven drug naive schizophrenic subjects, eight first episode schizophrenic subjects who showed a good therapeutic response to quetiapine treatment and eight normal controls were matched for age and sex underwent a single FMRI scanning session in a 1.5T scanner. During this they completed 1) a blocked periodic overt verbal fluency task (generation of single words in response to a letter cue) 2) passed motor task (random movement of a manual joystick) 3) task involving passive auditory and visual stimulation. Results Comparing the two patient samples the quetiapine treated group exhibited significantly greater power of activation in network of areas that included the inferior frontal cortex (Broca area) and supplementary motor area ($p<0.05$). No significant differences in activation between the patient groups were seen in the passive sensory stimulation task. Despite symptomatic recovery in the quetiapine treated group activation during the two active tasks did not normalise completely compared with the healthy control group. Discussion Quetiapine selectively enhances activation during a cognitive task dependent on frontal cortex function and hence this effect is unlikely to be a general action of quetiapine on cerebral blood flow. Differences in activation between the quetiapine treated and healthy control groups may reflect cognitive

impairments that persist even after good symptomatic recovery in first episode schizophrenia.

FUNCTIONAL CONNECTIVITY OF INNER SPEECH IN SCHIZOPHRENIA

R. A. Kanaan,* S. Shergill, E. Amaro, M. Brammer, R. Murray, P. McGuire
Psychological Medicine, Institute of Psychiatry, London, London, United Kingdom

We explored fronto-temporal connectivity using fMRI of patients and controls generating inner speech. Method The subjects were eight schizophrenic patients in remission recruited from the wards and clinics of the Maudsley Hospital, and 8 controls matched for age, sex and IQ. Diagnosis was made by clinical interview and case-note review, using DSM IV criteria. All subjects were trained to overtly say the word 'rest' once per second and once every four seconds. When they had demonstrated stability of this, they were asked to do the same covertly. Before and after the scan, their silent speech rates were monitored by asking them to tap their finger at each covert speech act. They were then scanned for 5 minutes in a 1.5T GE Signa MRI while covertly repeating the word for alternating 30 second blocks at 1Hz and 0.25Hz in an AB design, without finger tapping. The desired rate was shown to subjects on a screen visible from the scanner. Image analysis was performed using XBAM. All individual maps were then entered into a conjunction analysis that selected only those clusters that were both significant, and whose significance was not due to the effects of the patient group or control group alone. Time series for these clusters were extracted at the individual level, and averaged over the sub-groups of patients and controls. Pearson correlations were calculated between averaged time-series for supra-threshold clusters in the areas of interest. Results The conjunction activation map showed greater left inferior and medial frontal cortex, left and right superior and middle temporal gyrus, at the faster rate, compared with the slower rate, of speech generation. The left inferior frontal lobe activation was significantly correlated with the left superior temporal lobe (0.264, p=0.008) and middle temporal lobe (0.315, p=0.001) in controls. In patients, the left inferior frontal lobe was more weakly correlated with the middle temporal lobe (0.268, p=0.007), but was not correlated with the superior temporal lobe when corrected for multiple comparisons. Discussion This method allows comparison of the same activation areas, selected from patients and controls as groups. Both groups showed widespread activation of the expected areas. Though frontal/superior temporal correlation was weak in the controls, it was not significant in the patients, supporting differential fronto-temporal disconnectivity in schizophrenia.

CONTEXT-PROCESSING DEFICITS AND DECREASED PREFRONTAL CORTEX ACTIVITY: SPECIFIC ASSOCIATIONS WITH UNMEDICATED, FIRST-EPISODE SCHIZOPHRENIA AND WITH DISORGANIZATION SYMPTOMS

J. G. Kerns,* A. W. MacDonald, D. M. Barch, A. Holmes, J. D. Cohen, C. S. Carter
Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

The goals of the research was to examine whether (1) individuals with schizophrenia experiencing their first episode of the disorder and medication naive exhibit both performance deficits and decreased prefrontal cortex activity on a context processing task; (2) context processing deficits were unique to schizophrenia and not associated with other psychiatric disorders; and (3) context processing deficits were uniquely associated with particular symptoms. There were three participant groups: (1) first episode of schizophrenia (n = 18), (2) non-schizophrenia psychoses control (e.g., people with mood disorders, n = 12), and (3) non-psychiatric control (n = 28). During fMRI, participants completed the A-X version of the continuous performance task (A-X CPT). In the A-X CPT, on every trial, participants see a cue and a probe letter, with the only target being an X probe preceded by an A cue. Because the majority of trials consisted of an A cue followed by an X probe, responding to an X as a target becomes a prepotent response. Thus, in this task, demand for cognitive control is increased whenever the cue is not an A (i.e., B trials) because with a B cue participants need to overcome the prepotent response of responding to the X as a target. Thus, fMRI data were analyzed with the general linear model to examine whether people with schizophrenia exhibited decreased prefrontal cortex activity to B cues. The results were that individuals with schizophrenia committed more errors on BX trials than did non-psychiatric controls. In addition, in comparison with both control groups, individuals with schizophrenia exhibited decreased prefrontal cortex activity in response to B cues. Furthermore, decreased prefrontal cortex activity was associated with increased disorganization symptoms. We conclude that individuals with schizophrenia exhibited poor performance and hypofrontality in a context processing task. These deficits are present at the onset of the disorder and are not confounded by the effects of medication or attributable to the effects of psychosis in general. Importantly, the finding of hypofrontality was unique to schizophrenia and was not found in a non-schizophrenia psychiatric control group. Moreover, context processing performance was also specifically associated with disorganization symptoms. Thus, the current results provide further evidence that impaired context processing and decreased prefrontal cortex activity are important aspects of schizophrenia.

FUNCTIONAL CEREBRAL DEFICITS DURING COGNITIVE PERFORMANCE IN FIRST-EPISODE SCHIZOPHRENIA PATIENTS: A MULTI-CENTER FMRI STUDY

M. Klein,* U. Habel, T. Kellermann, K. Koch, D. Braus, T. Frodl, B. Kaufmann, T. Kircher, E. Meisenzahl, B. Müller, M. Müller, S. Ruhrmann, I. Tendolkar, R. Thienel, R. Schlösser, M. Wagner, F. A. Henn, H. Sauer, F. Schneider
Department of Psychiatry and Psychotherapy, University of Düsseldorf, Düsseldorf, Germany

Objective: In the context of this ongoing multi-center project, 44 first-episode schizophrenia patients and 44 healthy controls (matched for gender, age and parental education) were investigated by means of functional Magnetic Resonance Imaging (fMRI) while performing a modified version of the Continuous Performance Test (CPT). Phantom measurements (Siemens standard phantom) are used for quality control. Method: Subjects perform a randomized sequence of 0-back and 2-back tasks, with an intermediate baseline task (fixation). The 0-back task requires attention capacities, while the 2-back task creates a demand on working memory abilities. Group analyses