into individual practices was carried out for the full year of the study. Group B (control group) will be educated in the second year.

The range of outcome variables being assessed include general practitioner's identification index, patient's outcome for depression, prescription of antidepressants, referrals to secondary care, suicide rates, and the cost effectiveness of the intervention. Methodological and practical issues will be presented.

S27. The brain imaging of psychopathology

Chairmen: S Hirsch, L De Lisi

SIMILARITIES AND DIFFERENCES BETWEEN SCHIZOPHRENIA AND AFFECTIVE DISORDERS

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Functional brain imaging techniques can be broadly divided into two categories: "brain mapping" procedures which measure regional cerebral blood flow or metabolism as an index of neural activity and radioligand studies which may be used to obtain measures of enzyme / receptor activity, density or affinity and possibly fluxes in endogenous neurotransmitters. To date only brain mapping techniques have been used extensively in the study of the neurophysiological correlates of psychopathology. Brain mapping studies in psychiatric patients have most commonly been used with a cross-sectional design to identify changes in the pattern of brain activity in patient groups in comparison with an appropriate control group. Patients have been scanned in an "activated" state while performing a task designed to highlight specific aspects of their psychopathology, or at "rest", in which case persistent symptomatology (such as depressed mood or hallucinations) is considered the activating state. In other studies the neurophysiological variable (e.g. regional cerebral blood flow) is correlated with a relevant measure of psychopathology within the patient group. These techniques have been used extensively in schizophrenia and to a lesser degree in patients with affective disorders. They have established with increasing reproducibility that distributed abnormalities of brain function occur in the major psychiatric disorders, with some relationship to symptom or syndrome profiles. Indeed there is some evidence that the overlap in results from cross-sectional studies in schizophrenia, depression and other affective disorders is due to the presence of common symptoms across diagnosis. The longitudinal comparison of patients before and after recovery is a conceptually simple but underused method of examining the relationship between cerebral dysfunction and psychopathology. Such studies have shown that lateral prefrontal cortical function in depression normalises with clinical recovery. The challenge for functional imaging is now to further probe these identified dysfunctions with more refined methods that have greater sensitivity and which may ultimately be able to define the relationship between a particular pattern of abnormal brain function, specific psychopathology and a biochemical mechanism. The progress that has been made in this endeavour and future strategies will be presented with particular reference to "brain mapping" activation studies in schizophrenia and depression and developments in radioligand studies.

FUNCTIONAL BRAIN IMAGING OF NEGATIVE SYMPTOMS OF SCHIZOPHRENIA

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Negative schizophrenic symptoms are poorly responsive to neuroleptic medication, and may be heterogeneous, since it is difficult to discriminate primary, enduring negative symptoms from those secondary to long-term neuroleptic treatment, depression, or institutionalisation. It has been hypothesized that they may be related to a deficient dopaminergic transmission, to a functional hypofrontality, or to structural abnormalities.

First, we studied negative symptoms and dopaminergic variables. In order to investigate the links between dopamine D2 (postsynaptic) receptors and primary negative symptoms, young, drug-free negative schizophrenics were selected. The measure of the striatal D2 receptors assessed by positron tomography (PET) correlated negatively to the score of a dimension of psychomotor poverty, involving the core negative symptoms alogia and blunting of affects [1].

At the presynaptic level, the dopaminergic function was studied with PET and 18F-FluoroDOPA, using the Patlak method in 6 non-neuroleptized schizophrenics and controls. The variance of the 18F-Dopa uptake constant Ki was significantly increased in patients: the 18F-Dopa uptake constant Ki was markedly increased in some, but not all, schizophrenics, and decreased in catatonia.

Second, the links between the negative symptoms and the cerebral regional activation abilities are currently studied using the $H_2{}^{15}O$ method, measuring the regional cerebral blood flow changes through lexical evocation tasks. In negative patients, preliminary results suggest a hypofrontality in the resting state, and preservation of the capacity to activate some frontal regions during the tasks, although with a somehow different pattern of regional activation than in controls.

[1] Br J Psychiatry 1994 164, 27–34.

FUNCTIONAL NEUROANATOMY OF VERBAL SELF-MONITORING

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Background: Cognitive psychological models and functional neuroimaging data suggest that auditory verbal hallucinations may result from the disordered monitoring of inner speech. However, the brain regions involved in normal verbal monitoring are unknown. We sought to identify them by examining the neural response to alterations in auditory verbal feedback during reading aloud, so that the speech that was perceived sounded different to the speech that was articulated.

Methods: Regional cerebral blood flow was measured with positron emission tomography and $H_2{}^{15}O$ while 6 dextral male controls articulated single words, presented at 2s intervals on a VDU. Each subject had 12 scans. The baseline task involved reading aloud and hearing one's own speech. Verbal monitoring was engaged in two conditions. In the first, the pitch of the subject's speech was elevated by 8 semitones with an acoustic effects unit. In the second, their speech was substituted with that of an investigator, who articulated the words in synchrony with the subject. The tasks were matched for volume of auditory input, and were presented in a counterbalanced order. Data were analysed with Statistical Parametric Mapping.

Results: Distorting subjects' speech (through pitch elevation) while they read aloud led to bilateral activation of the cortex around the superior temporal sulcus ($p < 0.001$), with a greater response on the right side than the left. A similar pattern of activation was evident when subjects read aloud, but heard the words in another person's voice instead of their own. The active tasks differed in that reading aloud with distorted feedback was also associated with activation in the left insula/operculum, whereas reading with alien feedback led to activation in medial prefrontal cortex ($p < 0.001$).

Conclusions: These data suggest that the monitoring of self-generated speech involves the temporal cortex bilaterally, in regions similar to those previously associated with the processing of externally-generated speech. The temporal localisation is consistent with the notion that functional abnormalities in this region in patients with auditory verbal hallucinations reflect a disorder of verbal self-monitoring.

DOPAMINE RECEPTORS AND NEUROLOGICAL SIDE EFFECTS

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Positron emission tomography (PET) and [11C] raclopride were used to quantify the degree of striatal D2 receptor occupancy induced by antipsychotic drug treatment. The degree of D2 receptor occupancy was related to antipsychotic effect as well as to extrapyramidal side effects (EPS).

In an open study of 22 patients treated with classical neuroleptics, the D2 receptor occupancy was very high (70–89%). Among patients with EPS, the D2 receptor occupancy was significantly higher. In a double blind dose finding study of 13 patients treated with raclopride, a significant relationship was found between the degree of D2 receptor occupancy and antipsychotic effect. Further, patients with EPS had significantly higher D2 receptor occupancy. The results confirm that there is a significant relationship between presence of EPS and degree of D2 receptor occupancy in the striatum.

A quantitative relationship between D2 receptor occupancy and EPS on one hand and antipsychotic effect on the other does not necessarily mean that there is a mechanistic relationship for these two observations. Among patients who benefitted from antipsychotic drug treatment only those in the higher range of D2 receptor occupancy were at risk for EPS. The results suggest that the threshold for antipsychotic effect is lower than the threshold for EPS. Further, EPS may appear within hours after a single dose of haloperidol following the time course for D2 receptor occupancy, whereas several days or weeks may elapse before antipsychotic effect occurs. These findings support the view that the neuronal events underlying antipsychotic effect and EPS may be distinct.

In 16 patients treated with the atypical antipsychotic clozapine, the D2 receptor occupancy was significantly lower (20–67%) than in patients treated with classical neuroleptics (70–89%). Clozapine is thus atypical with regard to degree of D2 receptor occupancy, a finding that may explain the lack of extrapyramidal side effects.

THE SENSORIMOTOR CORTEX AND SUPPLEMENTARY MOTOR AREA IN SCHIZOPHRENIA: A STUDY WITH FUNCTIONAL MAGNETIC RESONANCE IMAGING

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Clinical studies indicate that motor performance is impaired in schizophrenia. To identify the underlying cerebral changes we investigated sensorimotor cortex and SMA activation under finger-to-thumb opposition using functional magnetic resonance imaging (fMRI). 10 DSM-III-R schizophrenics and 7 healthy controls were included. All subjects were right-handed. fMRI was performed using a 1.5 Tesla Siemens scanner. Scans were obtained in a resting condition followed by an activation state (finger-to-thumb opposition) and the activities in the sensorimotor cortices and SMA recorded. All subjects showed a significant activation of the SMA, and both, ipsilateral and contralateral sensorimotor cortices. In the controls, ipsilateral finger-to-thumb opposition lead to a greater left than right hemispheric sensorimotor cortex coactivation. When compared with the healthy controls, the schizophrenic patients showed a decreased activation of both, sensorimotor cortices and SMA, as well as a reversed lateralization effect.

Our second study was designed to investigate the relation between motor performance and brain activation. 10 healthy, right-handed volunteers were included. To monitor motor performance a pronation/supination device was adapted to the fMRI-environment. Probands were asked to pronate/supinate their forearm according to the pace given by a metronom (25, 50 and 75 strokes per minute). Pronation/supination led to a significant activation of the contralateral and ipsilateral sensorimotor cortices and the SMA. Accelerated speed led to a significant increased activation of the right ($df = 2$; $F = 3.48$; $p < 0.05$), but not left ($df = 2$; $F = 1.19$; $p = 0.32$) sensorimotor cortex. On both hemispheres, contralateral pronation/supination ($df = 1$; $F = 20.07$; $p < 0.0001$) induced a significantly greater activation than ipsilateral pronation/supination ($df = 1$; $F = 40.36$; $p < 0.0001$). Regarding the SMA, a significant velocity effect was not observed.

Our studies indicate that sensorimotor cortex and SMA dysfunction contribute to motor disturbances in schizophrenia. While significant velocity effects were restricted to the right sensorimotor cortex, our second fMRI-study also demonstrates that the pronation/supination device is suitable to monitor task during fMRI-acquisition.

PASSIVITY PHENOMENA IN SCHIZOPHRENIA

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Movement disorders are described in schizophrenia prior to the advent of neuroleptics, in untreated cohorts, and in 'preschizophrenic' children. Patients with passivity phenomena make more motor errors than other schizophrenics. We hypothesized that in patients with delusions of passivity, willed movement would be associated with aberrant activity in distributed neural networks subsuming motor control. We obtained and analyzed PET derived measures of regional cerebral blood flow from a motor [joystick] activation paradigm; comparing externally paced, freely selected [right hand] movement with stereotyped [externally specified] movement and rest. 7 Schizophrenics, experiencing passivity phenomena, in new treatment episodes, 6 schizophrenics without such phenomenology, and 6 normal volunteers were studied. All were males. Response times and 'randomness' of response showed no significant differences. Statistical parametric mapping demonstrated underactivation of motor, lateral premotor cortex and basal ganglia, and overactivation of medial premotor cortex in those subjects with passivity [relative to both 'control' groups]. These differences were reduced with symptom resolution. These data support the hypothesis that distributed motor systems are dysfunctional in schizophrenics with delusions of passivity. We are conducting further work to determine the contribution of syndromal diagnosis.