Relevance of brain imaging studies for social psychiatry

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Computerised tomography (CT) and magnetic resonance imaging (MRI) have dramatically changed diagnostic work-up in neurology. Clinical psychiatry has profited from the potential of both diagnostic tools in ruling out focal intracranial pathology (Becker *et al.*, 1995). Also, a multitude of research studies covering the whole range of psychiatric disorders using CT, MRI, magnetic resonance spectroscopy (MRS), positron emission tomography (PET) and single photon emission computed tomography (SPECT) have been published in recent years. MRI, in comparison with CT, has enhanced diagnostic accuracy, particularly in the middle and posterior cranial fossa. Its advantages include an increase in diagnostic sensitivity, free choice of imaging plane, better differentiation of grey and white matter as well as basal ganglia morphology. However, specificity of findings is limited, e.g. where white matter hyperintense lesions are concerned (Becker *et al.*, 1995). SPECT and PET permit the study of cerebral blood flow, regional brain metabolism and neurotransmitter receptor or transporter densities. Both methods require the administration of radioactive tracers, and functional images are produced on the basis of photon or positron emission. PET imaging requires on-site availability of a cyclotron unit to produce adequate tracer substances (with short half-lives) which makes the method inherently expensive.

Brain MRS in psychiatry is still in its infancy, and most studies have been performed using ^{1}H and ^{31}P, while some have used ^{7}Li and ^{19}F. The first generation of MRS studies, in schizophrenia, have illuminated some pathophysiological aspects. Noteworthy findings include reduction in N-acetyl aspartate (a marker for neural integrity) in the temporal lobe and evidence of membrane alterations in prefrontal and temporal cortices. In the affective disorders, ^{31}P MRS demonstrated alterations in the phosphomonoester resonance in bipolar disorder as well as alterations in the high-energy phosphates in bipolar and unipolar depression. ^{19}F and ^{7}Li MRS, in affective and non-affective psychotic disorders, have also been used to determine brain drug concentrations (e.g., trifluoperazine, fluphenazine, fluoxetine, and lithium) (Keshavan & Pettegrew, 1997).

Functional MRI (fMRI) will increasingly become the key functional imaging tool (Kindermann *et al.*, 1997). It is based on the functional link between neural activity and brain perfusion; activation of neurons leads to an increase in regional cerebral oxygen demand. Regional perfusion is enhanced to meet this demand which leads to a net increase in local oxygen concentration, particularly in draining veins. This leads to a shift of balance in the ratio between oxyhemoglobin and deoxyhemoglobin favouring the latter — a paramagnetic substance. This blood oxygen-level dependent (BOLD) contrast can be visualised due to a reduction in magnetic susceptibility which results in signal increase. Experimental stimulation paradigms are used to test functional neural activation. Resting state and active state (and/or different active states) are compared, and sophisticated statistical methods help in assessing activation differences. Study designs which are used in functional brain imaging research include: (a) categorical approaches in which patients and control subjects are compared, (b) parametric experimental designs which are based on the evocation of physiological responses by the systematic variation of an independent (cognitive or behavioural) variable, or (c) factorial experiments which examine interactions between variables in different domains of either cognition, behaviour or external manipulation, for instance by pharmacological agents. These designs can also be combined in clinical studies (Dolan & Friston, 1997).

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STRUCTURAL IMAGING FINDINGS

Increased ventricular size is one of the best replicated findings in schizophrenia research, and there is additional evidence of increased external cerebrospinal fluid (CSF) spaces in patient groups. However, a variety of studies have shown these findings not to be specific to schizophrenic disorders, and widening of internal and external CSF spaces has been described also in bipolar affective and schizoaffective disorders. Brain regions in which structural deficit has been reported in patients with schizophrenia include the frontal lobe, temporal lobe and cerebellum (Chua & McKenna, 1995). Such brain structural abnormalities may be acquired early in life and constitute an unspecific vulnerability marker. Some studies have shown progressive brain structural change in a subgroup of patients which might reflect an active brain disease process (DeLisi *et al.*, 1997, Nair *et al.*, 1997).

CLINICAL CORRELATES OF STRUCTURAL BRAIN ABNORMALITIES

Poor premorbid adjustment may predict reduced cerebral volume and/or increased sulcal volume in patients with schizophrenia (Harvey *et al.*, 1993). A number of studies have looked at clinical correlates of brain structural abnormalities, particularly in schizophrenia. Some described associations of frontal atrophy or ventricular enlargement and a poor response to neuroleptic treatment or overall poor clinical outcome (Andreasen *et al.*. 1982). Van Os *et al.* (1995) found an association of structural deficit on CT/MRI with poor cognitive function and unemployment. Also, a negative association was reported between the extent of white matter hyperintense lesions on MRI and treatment response in depressed patients (Hickie *et al.*, 1995). Figiel *et al.* (1991), in a further MRI study, reported the risk of neuroleptic-induced parkinsonism to be increased in patients with striatal white matter hyperintense lesions.

REGIONAL BRAIN DYSFUNCTION-SPECT, PET AND FMRI

In regional cerebral blood flow (rCBF) and PET studies reduced frontal blood flow and a decrease in frontal glucose metabolism have been described in patients with schizophrenia. However, studies have not been unanimous with respect to 'hypofrontality' or altered anterior-posterior gradients. With regard to laterality, most studies have found either no hemispheric asymmetries or increased metabolism or blood flow in the left hemisphere, particularly in temporal areas (Swanson *et al.*, 1997). Alterations in striatal D2 receptor density in brains of people suffering from schizophrenia have not been firmly established so far (Okubo *et al.*, 1997). However, recent work has used functional approaches and resulted in findings of striatal D2 receptors being associated with negative symptoms in schizophrenia (Martinot *et al.*, 1994), and also in associations of prefrontal D1 receptors and cognitive deficits (Okubo *et al.*, 1997). Other studies found associations of dysfunctional thalamic-prefrontal circuitry and cognitive deficits (Andreasen *et al.*, 1996, Buchsbaum *et al.*, 1996).

Two recent studies using SPECT and PET demonstrate the degree of spatial resolution and syndrome differentiation which can be attained using these functional imaging methods. Ebmeier *et al.* (1997) found global depression severity and an independent 'vital depression' factor to be associated with increased perfusion in cingulate and other paralimbic areas, while an 'anxious depression' factor appeared to be associated with reduced frontal neocortical perfusion. In a study combining PET and MRI, Drevets *et al.* (1997) found an area of abnormally decreased blood flow (in resting state) in the subgenual prefrontal cortex in both familial bipolar and unipolar depressed patients. This decrease in perfusion, however, was at least partly explained by a corresponding reduction in cortical volume, as MRI demonstrated reductions in mean subgenual grey matter volume of 39 and 48% in the bipolar and unipolar patients, respectively. This brain region has been implicated in the mediation of emotional and autonomic responses to socially significant or provocative stimuli.

A highly circumscribed region of the left medial prefrontal cortex was found to be impaired in patients with Asperger syndrome (a mild variant of autism) characterised by deficits in the 'theory of mind' domain (understanding other people's minds; Happé *et al.*, 1996). Tamminga *et al.* (1992) demonstrated correlations of decreases in thalamus, frontal and parietal cerebral metabolism in schizophrenic patients with predominant negative symptoms. Dorsolateral prefrontal cortical dysfunction was reported by Dolan *et al.* (1993) to correlate with psychomotor retardation and cognitive deficits. This applied to patients with the syndromes of psychomotor poverty and

psychomotor retardation irrespective of whether they met diagnostic criteria for a schizophrenic disorder or depressive episode. The authors argued that their findings supported the view that the study of symptoms, or symptom clusters, could provide information additional to that of traditional diagnostic systems in studying the major psychoses. Symptoms such as delusions or hallucinations could also be studied by functional neuroimaging. A recent fMRI study found the response of the temporal cortex to exogenous auditory stimulation (speech) markedly reduced while patients were experiencing hallucinations (David *et al.*, 1996).

TREATMENT EFFECTS AND BRAIN IMAGING

Normalisation in cerebral glucose metabolic rate in the caudate nucleus has been described in patients with obsessive-compulsive disorder after successul behaviour therapy (Schwartz *et al.*, 1996). Remission of depressive states is associated with blood flow increases in left dorsolateral prefrontal cortex and medial prefrontal cortex including the anterior cingulate (Bench *et al.*, 1995). In a fMRI study before and during successful antidepressant treatment symptomatic improvement in two patients was accompanied by changes of blood flow activation in response to pictures with positive or negative emotional connotations. After two weeks of treatment an area of activation emerged in the right secondary visual cortex upon presentation of 'positive pictures' which had not been present while patients were depressed and anhedonic (Kalin *et al.*, 1997). Mayberg *et al.* (1991), in a case report, found a 25% increase in left temporal cortical serotonin (5-HT_2) receptor binding using ^{11}C-N methyl spiperone and PET after spontaneous remission of post-stroke depression. Where antipsychotic medication is concerned, associations between neuroleptic treatment and increased striatal/basal ganglia metabolic rate have been a common finding, and this applies to both typical and atypical neuroleptics (Swanson *et al.*, 1997).

SOCIAL FUNCTIONING AND NEURAL SYSTEMS

Kopelowicz and Liberman, in their foreword to 'Cognitive Rehabilitation in Neuropsychiatry' edited by Corrigan & Yudovsky (1996), argue that a new paradigm is emerging in rehabilitation psychiatry. The rehabilitation model directs attention to the functional capabilities and community adaptation of the mental health consumer rather than focusing on individual disease-specific symptoms. Corrigan & Yudovsky (1996), in their book, bridge the gap from these complex measures of overall social adaptation to the issues of cognitive dysfunction and specific intervention techniques.

Premorbid low intellectual ability could be a risk factor for schizophrenia and other psychoses; David *et al.* (1997) found the risk for schizophrenia to vary with performance and mechanical knowledge tasks. Thus, in their large-scale epidemiological study of Swedish conscripts followed up over more than 10 years composite measures of cognitive function were associated with morbid risk. Recent research in schizophrenia underlines the importance of cognitive deficits for social functioning and community adaptation (Green, 1996). Cognition is clearly dependent upon activity within distinct neural systems. This would suggest that social functioning and brain activity are inter-related, and studying both domains jointly may open new perspectives to psychiatric research.

Modern imaging studies provide access to physiological and dysfunctional cognitive processes, and they have improved our understanding of pathogenetic mechanisms in the major psychoses. Prior to and parallel with the development of such new diagnostic tools there has, in the last fifty years, been a paradigmatic shift in psychiatric practice. The field has moved away from long-term institutional care towards therapeutic environments which tend to be small-scale, emphasise skill development and patient autonomy (Leff, 1997). They aim to target patients' needs and adapt flexibly to changing clinical and social circumstances (Knudsen & Thornicroft, 1996). On the other hand, there has been a trend towards providing more specific treatment programmes to patients with a variety of disorders. Such efforts, in the functional psychoses, include integrated psychosocial treatment programmes, social skills training, family treatment interventions, and elaborate coping programmes for patients with persistent delusions or hallucinations (Anderson & Adams, 1996, Brenner *et al.*, 1996, Drury *et al.*, 1996, Penn & Mueser, 1996). Targeted treatment interventions require the identification of criteria which help to decide whether or not a particular intervention may help individual patients or patient groups.

As this model of service provision has evolved the importance of identifying response predictors and

evaluating outcome has also been emphasised (Becker & Thornicroft, 1998). The availability of targeted interventions may help in organising 'packages of care' which are time-limited, make the best use of resources and interfere relatively little with daily living routine. To mention an example in a group exposed to extreme and often long-term physical and psychological stress, Susser *et al.* (1997) have described a 'critical time intervention' of a few weeks in the homeless mentally ill in New York and found lasting positive effects on outcome at follow-up. Information on predictors of treatment success or failure is highly valuable where one or a range of such specific interventions are available.

From an overall perspective, the framework of psychiatric services offered to patients needs to be culturally adequate, clinically reasonable and geared towards people's social needs. On the other hand, response predictors may be relevant in deciding which specific elements should be added to a generic 'package of care'. Patients or service users might well ask for such evidence in the future, and are likely to become key stakeholders in the research process. Continuous dialogue between professionals and service users in planning the care process and an increasing scope of sophisticated single-case designs could thus converge in the future. Using modern functional neuroimaging we may be able to better understand cognitive and behavioural deficits in people suffering from schizophrenia and other functional psychoses, and we may soon be in a position to plan and implement this type of research jointly with patients in order to improve coping skills and jointly develop therapeutic programmes tailored to patients' needs.

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