seminars in **THE NEUROSCIENCES**, Vol 7, 1995: pp 165–171

Functional imaging and the neurobiology of the psychoses

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The neurobiology of the psychoses has been a controversial issue. Functional imaging techniques now provide a powerful tool to address critical questions concerning their fundamental nature. It is argued that the core abnormality is a disorder of brain function. *These functional deficits are regionally specific and mediate their effects through a disruption of cognitive processes which manifest in symptoms that provide the descriptive basis for the psychoses. There are no unequivocal accounts of the mechanisms of brain dysfunction though it is suggested that in schizophrenia a critical component is a disorder of cerebral integration. Preliminary evidence that bears on this issue is discussed.*

Key words: cognitive / functional / imaging / psychosis

"In every insanity there is morbid affection of more or less of the higher cerebral centres, or synonymously, of the highest level of evolution of the cerebral sub-system or, again synonymously, of the anatomical substrata, or physical basis, of consciousness. There may be discoverable disease destructive of nervous elements, or there may be loss of function from some undiscovered pathological process inferred from symptoms." Hughlings Jackson (1894)

The functional psychoses, depression and schizophrenia, are primarily disorders of consciousness. The neurobiology of these conditions remains the most challenging issue in clinical neuroscience. The capability of going beyond the level of clinical description to a direct examination of the functioning brain has long been considered a necessary condition for an understanding of the psychoses. Initial steps in this direction can be traced to the pneumoencephalographic (PEG) investigations of Jacobi and Winkler (1927).[1] The current availability of sophisticated non-invasive imaging techniques, providing detailed information on brain structure and function, means that the neurobiology of the psychoses is open to direct empirical investigation. There are two emerging perspectives from imaging studies. One perspective, derived from structural studies, is that these disorders are characterized by a fixed pathology manifesting in morphological brain changes. An alternative perspective is that the critical abnormality is a disorder of brain function or brain physiology. This latter perspective derives from studies based on functional imaging techniques. The evidence that the psychoses are manifestations of disorders in brain function provides the subject matter for the present article.

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1044-5765/95/030165+07 $8.00/0

The functional anatomy of the psychosis

The term functional refers to organized brain systems that provide the substrate for behaviour and cognition. A functional abnormality in the psychoses is suggested by their relapsing and remitting course, the fluctuations in the expression of critical symptoms and the responsiveness to pharmacological interventions. An important question therefore is what are the associated neurophysiological changes and do they implicate specific brain regions? One way to address this question is to compare patients with one of the categories of psychosis and matched controls using an index of cerebral physiology. A great many studies of this kind, based upon unconstrained resting state measures of cerebral physiology such as regional glucose metabolism (CMRGlu) or regional cerebral blood flow (rCBF), have been reported.

Schizophrenia, the most disabling of the psychoses, is characterised by an early age of onset, symptoms such as delusions, hallucinations, disordered thinking, impoverishment of action and, in many instances, a chronic course. It is defined phenomenologically and may subsume a number of clinical syndromes. In this respect it is a multidimensional disorder and consequently a distributed pattern of regional brain abnormalities is to be expected. It is not surprising therefore that a wide range of abnormalities are reported that include both overactivity or underactivity of regional brain function involving the prefrontal cortex[2-5], the basal ganglia[6,7] and temporal cortex[7-9].

Clinical depression is the most ubiquitous of psychiatric disorders. Its characteristic features, like those of schizophrenia, are multidimensional and can

include a disorder of mood, motivation, self evaluation, motor function and cognition. The findings from studies in depression have a greater consistency than those reported in schizophrenia. Decreases in regional brain function have been found in the dorsolateral prefrontal cortex and medial prefrontal cortex, the parietal cortex and temporal cortex.[10-17] Increases in regional brain function, especially in the frontal areas, have also been reported.[18,19]

The findings therefore indicate a range of regional brain abnormalities in both schizophrenia and depression. A notable feature is a lack of consistency across studies and the absence of any single deficit or pattern of deficit that defines one or other of the major psychoses. The absence of clear patterns of deficit across studies could be explained on the basis of differences in patient selection, the confounding effects of medication or aetiological heterogeneity. A simpler explanation is that the inconsistencies relate to differences in the behavioural or mental states of patients, both within and between studies. This suggestion means that the symptom profile of the patients is a variable of equal or perhaps greater importance than diagnostic category in resting state functional imaging studies.

Symptom profiles and regional brain physiology

Depression and schizophrenia are defined principally by the presence of combinations of symptoms. This clinical heterogeneity, in terms of symptom expression, has led to a call for a shift of focus in research 'to clinicopathologic correlations of specific psychopathologic domains with discrete neural circuits'.[20] Implicit in this proposal is the suggestion that regional brain function in the psychoses is related to symptom patterns. A corollary is that symptoms, which reflect current mental state, and brain function are tightly coupled. The evidence from studies of normal brain function provide strong evidence that mental state or set has a significant effect on brain physiology.[21,22] Can the diversity of findings in 'resting state studies' of depression and schizophrenia therefore be explained on the basis of a variability in the mental states of patients within and across studies?

A relationship between symptom profile and brain function in the psychoses has been demonstrated using correlational techniques.[23,24] In schizophrenia a syndrome of disorganization (with symptoms of incoherent speech and inappropriate affect) is associated with increased blood flow in the anterior cingulate cortex and thalamus and decreases in the inferior parietal cortex bilaterally. A syndrome of reality distortion (with symptoms of hallucinations and delusions) is associated with increased blood flow in the left parahippocampal gyrus and ventral striatum and decreased blood flow in the posterior cingulate. A syndrome of psychomotor poverty (with symptoms of paucity of speech and action) is associated with increased blood flow in the striatum and decreased blood flow in the left dorsolateral prefrontal cortex and left superior parietal cortex.[23] In depression symptoms of anxiety and agitation are associated with increased blood flow in the posterior cingulate cortex and inferior parietal cortex bilaterally. Symptoms of decreased speech and action are associated with decreased perfusion in the left dorsolateral prefrontal cortex and psychomotor retardation is associated with decreased blood flow in the left dorsolateral prefrontal cortex and left angular gyrus. Finally, impaired cognition characterized by memory and attentional deficits, is associated with decreased blood flow in the medial prefrontal cortex.

A striking observation is that in two different diagnostic categories, depression and schizophrenia, there is a relationship between dorsolateral prefrontal hypoperfusion and a similar dimension of psychopathology characterized by psychomotor dysfunction. Psychomotor retardation in depression and psychomotor poverty in schizophrenia share many features in common. For example, the symptom of poverty of speech is highly correlated with syndromes of psychomotor poverty in schizophrenia[25] and psychomotor retardation in depression.[26] This suggests that similar symptomatic expression in the psychoses is due to a common underlying pathophysiology. This hypothesis has been explicitly tested by pooling the data from two separate studies of depression and schizophrenia. Poverty of speech, defined as a 'restriction in the amount of spontaneous speech, so that replies to questions tend to be brief, concrete and unelaborated', provided the common measure across diagnosis of diminished psychomotor activity. In the pooled study, poverty of speech predicted relative left-sided dorsolateral prefrontal cortex hypoperfusion while diagnosis had no predictive power. Furthermore, the effect of poverty of speech was entirely independent of diagnosis.[27] In other words the association of decreased rCBF in the left dorsolateral prefrontal cortex was with a symptom and not with a diagnosis.

State or trait abnormalities?

The evidence that the pattern of blood flow in the psychoses relates to symptoms rather than diagnostic category implies that regional brain abnormalities are state rather than trait related. This has two important implications. Firstly, patterns of 'resting' blood flow should normalize with symptomatic remission. This is difficult to study in patients with schizophrenia as the course of the illness is often chronic. However, in depression, symptom remission is associated with a relative normalization of resting blood flow patterns.[28] Secondly, blood flow patterns in steady state or resting studies of psychiatric patient populations do not reflect the mind 'at rest', but rather the mind functioning abnormally. This suggestion is easy to grasp in a situation where patients experience hallucinations or other positive symptoms during the scan. In this situation the pattern of neural activity reflects the associated brain state. It is less easy to grasp why a clinical state associated with poverty of speech should be associated with decreased activity in a resting scan. However, it is readily explicable within a cognitive account of poverty of speech. Here the symptom of poverty of speech reflects a more general deficit in the initiation of spontaneous acts of any kind including speech and internal thought processes. In an unconstrained context, such as lying in a scanner, there is good evidence that normal volunteer subjects will inevitably generate spontaneous thoughts or inner speech.[29] Inner speech is an activity almost certainly associated with frontal activation and it is this spontaneous mental activity, and its associated neural activity, that is reduced in patients with poverty of speech.

The cognitive anatomy of symptoms

A cognitive analysis of psychopathology proposes that symptoms are a manifestation of a breakdown in normal cognitive processes. An elegant account of this perspective with reference to schizophrenia has been provided by Frith.[30] The heuristic value of this approach is its predictive power. Functional specialization in the human brain implies that discreet cognitive processes can be attributed to particular functional architectures. Symptoms represent a breakdown of one or other cognitive process and logically the brain system involved should be that which mediates the associated cognitive process. The syndrome of psychomotor impairment serves as a useful illustration of this approach which is summarized in Figure 1.

In patients with psychomotor retardation or poverty the core difficulty is initiating action with a consequent restriction of both verbal and motor expression. For example, patients with the syndrome will give normal responses to questions, albeit slowly, but generate little in the way of propositional speech. Kraepelin[31] undoubtedly had this phenomenon in mind when he described dementia praecox, his term for schizophrenia, as resulting in 'failures of mental activities, loss of mastery over volition, of endeavour, and of ability for independent action'. This, in effect, amounts to a cognitive level description where symptoms are conceived as representing an impairment of intentional or willed behaviour or 'loss of mastery over volition'. As already described this syndrome is associated with decreased function in the dorsolateral prefrontal cortex. What is the putative underlying cognitive process? Its core symptoms can be conceived of as a disorder of intentional behaviour or willed action. Intentional or willed behaviours can be operationally defined as those associated with conscious selection that is relatively independent of external guidance. Studies in normal subjects have demonstrated that willed action engages the dorsolateral prefrontal cortex.[32] Thus at the brain system level, willed action and disorders of willed action as represented by syndromes of psychomotor impairment are both related to the function of the same brain system.

Psychological challenge in patients with psychoses

Rather than scanning during 'rest', where the associated neurophysiology is predicted by symptoms present at the time of scanning, it is possible to have patients perform a task during the scan. This controls, to some extent, the mental state of the patient such that differences in the pattern of blood flow, are less likely to be due to differences in the current symptomatology. In implementing this type of approach a task can be chosen that physiologically engages a target brain area. This type of approach has been used extensively by Weinberger and colleagues who studied patients while they performed a version of the Wisconsin Card Sorting Test (WCST).[33-35] This task is sensitive to frontal lobe lesions.[36] The reported studies have consistently demonstrated that normal subjects display significantly greater activity in frontal

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