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ADVANCES IN NEUROPSYCHIATRY

Functional brain mapping of psychopathology

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In this paper, we consider the impact that the novel functional neuroimaging techniques may have upon psychiatric illness. Functional neuroimaging has rapidly developed as a powerful tool in cognitive neuroscience and, in recent years, has seen widespread application in psychiatry. Although such studies have produced evidence for abnormal patterns of brain response in association with some pathological conditions, the core pathophysiologicals remain unresolved. Although imaging techniques provide an unprecedented opportunity for investigation of physiological function of the living human brain, there are fundamental questions and assumptions which remain to be addressed. In this review we examine these conceptual issues under three broad sections: (1) characterising the clinical population of interest, (2) defining appropriate levels of description of normal brain function, and (3) relating these models to pathophysiological conditions. Parallel advances in each of these questions will be required before imaging techniques can impact on clinical decisions in psychiatry.

which the issues of disease classification and the application of functional imaging are especially pertinent. However, the issues generalise to all activation studies in all contexts, and we do not aim to comprehensively review the published literature to be found elsewhere.^{2–5} To constrain the scope of the review, we implicitly adopt a somewhat restricted definition of brain function, to include studies focusing on the haemodynamic index of neural activity; this will necessarily exclude a substantial literature which provides additional and important insights in psychiatry—for example, the use of radioisotopes to identify receptor occupancy in psychiatric conditions.^{6–8} Finally, our focus on imaging techniques coupled to vascular reactivity points to several issues of interpretation, such as the quantitative relation between single neuron recordings and haemodynamic indices of neuronal activity,⁹ the effects of major vessels draining activated areas,¹⁰ the insensitivity of haemodynamic techniques to disambiguate between neuronal excitation and inhibition, and the temporal delay between neural activity and local vascular response. Such issues are reviewed elsewhere.^{11 12}

CRITERION 1: HAS THE PSYCHIATRIC DISORDER UNDER STUDY BEEN APPROPRIATELY SPECIFIED?

Case-control designs

The ultimate validity of a case-control methodology, in which diagnostic category is a necessary and sufficient inclusion criterion, hinges upon the validity of the taxonomy used. However, psychiatric conditions are, in reality, extremely difficult to define as discrete and homogenous entities. This fundamental difficulty surely contributes substantially to the inconclusive aspects of the current literature which has tended to use predominantly case-control designs. This is a problem that is relevant (although by no means uniquely so) to functional imaging studies of schizophrenia. Bentall *et al*^{13–15} for example, argue that over 100 years of schizophrenia research has been misconceived, as the concept has fallen short of the requirements of validity and reliability necessary to justify its existence as a scientific construct. Two patients diagnosed with the illness may have no symptoms whatsoever in common. Strauss and Summerfelt¹⁶ suggested that “Group comparison studies, using summarising statistics, the ‘normal science’ in schizophrenia research, may at times be misleading if not inappropriate.” Such group summary data are crucial to PET studies and almost ubiquitously used in fMRI studies. Bentall¹⁴ phrases the problem simply: “the comparison of one group of people who in all probability have nothing in common with another group of people who also probably have nothing in common.”

DEFINING THE QUESTIONS IN NEUROPSYCHIATRIC IMAGING

The aim and scope of this review is primarily a theoretical consideration of the emerging conceptual challenges germane to psychiatric functional imaging. We consider the difficulties that accompany the most frequent application of these techniques—an attempt to identify responses of the brain to changing tasks or contexts—and explore how these responses are affected by psychiatric illness. Such an approach stands or falls according to three criteria: (1) Has the psychiatric disorder under study been appropriately specified? (2) Has the chosen task enabled a clear and unambiguous manipulation of the psychological processes that we wish to study? (3) How may we interpret changes in brain activations in the patient group—do they reflect a cause of, a consequence of, or a compensation for the impaired psychological state?¹

These are critical issues. If they cannot be addressed, functional imaging approaches must confine their ultimate aims to diagnosis and accept that they will never clarify aetiology. If the questions remain unanswered, the techniques, no matter how complex their technical advances, will inevitably produce ambiguous findings.

These key questions will be explored with particular emphasis on schizophrenia research, for

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The manifestation of clinical heterogeneity in research findings is well illustrated, for example, in imaging studies of frontal lobe function in schizophrenia, in which a case-control design has been adopted. An early study¹⁷ showed evidence of a reversal of the anteroposterior gradient of cerebral blood flow evident in healthy controls, a phenomenon which was termed “hypofrontality”. Numerous subsequent studies of resting state regional cerebral blood flow (rCBF) in schizophrenia have provided supporting evidence.^{18–31} However, many studies have been reported which failed to find evidence of hypofrontality, or indeed have found a hyperfrontal response in schizophrenic patients.^{32–42}

The concept of hypofrontality has clearly proved to be a useful focus of scientific investigation, and has led to increased understanding of the relation between behaviour and brain function, and the breakdown of this relation during psychosis. However, the inconsistencies evident in this field cannot be ignored, and must lead us to question the basic concepts which underlie the definition of disorder employed in these studies. Functional imaging is the latest in a long series of scientific techniques to be applied to the question of the biological basis of schizophrenia. Given the failure of any of these methodologies to provide a clear understanding of pathophysiological mechanisms, it is increasingly likely that the conceptualisation of the disorder is not a meaningful construct for which a scientific explanation of aetiology can be formulated: “As long as we are not able to disentangle the heterogeneity question at the clinical level, it is not likely that heterogeneity at the aetiological and pathophysiological levels can be resolved.”⁴³

The symptom oriented approach

To limit the assumptions implicit in case-control designs, imaging research has alternatively focused on the individual symptoms of psychosis. In addition to avoiding the problems highlighted with disease level categories, the symptom approach is proposed to represent a closer conceptual affinity with development from animal models, as this avoids the requirement of the model to account for heterogeneous disease categories in humans. For example, Costello⁴⁴ suggests that basic neuroscience research on biological mechanisms of reward and learned helplessness has progressed rapidly in terms of its application to the understanding of anhedonia as an individual symptom, but not as a model of depression. This has implications across diagnostic categories, beyond the clear link to loss of interest in depression, to affective symptoms in schizophrenia, and the reward basis of substance misuse. In accordance with such arguments, some functional imaging studies have adopted the symptom approach to neuropsychiatric research, to considerable gain—for example, focusing on auditory hallucinations,^{45–46} delusions of passivity,⁴⁷ and attributional bias.⁴⁸ Of course, functional imaging research will have very different implications depending upon whether measurements are made during the occurrence of the symptoms or not. If they are, then one has to contend with the interference of the symptom (and other symptoms presenting concurrently) with any cognitive process which may be engaged during experimentation. However, a focus on the remission phase of the illness would preclude certain symptoms from study which are amenable to treatment, but could equally be regarded as fundamental.

The assumption that individual psychotic symptoms are pure concepts of determined validity which can be reliably identified may be no more tenable than for diagnostic categories. Mojtabai and Rieder⁴⁹ argued that previous studies showed that reliability was higher for the diagnosis of schizophrenia than for the individual symptom items. Individual symptoms have also been shown to be of little prognostic value, and show a low rate of heritability, in comparison to diagnostic categories. Symptoms of psychosis, similar to

disease categories, are complex, varying in form, intensity, duration, and stability. Thus their assessment, and use as grouping variables in functional imaging research, is not straightforward: “Just as syndromes are constructs in need of validation, so are symptoms”.⁴⁹ Ultimately, symptom oriented research must impact on our understanding at a syndromal level, and inform disease level classification, given that individual symptoms, even those induced pharmacologically, do not occur in isolation, but as a component of a complex, dynamically variable, phenomenological presentation.

The familial/sporadic distinction

Another categorical distinction which has been used in psychiatric research to provide subgroups of greater homogeneity is the heuristic distinction between patients with familial history of the disorder, presumed to be of genetic origin, compared with those with sporadic presentation, presumed to be of environmental origin.^{50–52} This distinction in schizophrenia overlaps with a neuropathological dissociation, in that cerebral pathology is generally found in the absence of genetic loading for the illness.^{51–53} The advantage of this distinction is that it avoids phenomenological subgroupings, and the associated problems inherent in this approach, and is more closely based on a possible aetiological indicator, genetic transmission. This distinction thus aims to “yield subgroups which, although not totally discrete, will be of substantially greater aetiological homogeneity.”⁵⁴

The question of exactly what pattern constitutes a positive family history, whether narrowly defined (as, for example, a first degree relative with psychosis requiring admission to hospital), or defined more broadly, is determined arbitrarily, and therefore may be of no greater reliability or validity than the diagnostic categories they aim to subdivide. Similarly, there is evidence of substantial variation in the recording of family history, which may also lead to misclassification of subjects. A further problem with this model however, is that it assumes that genetic and environmental factors are relatively independent, whereas the occurrence of obstetric complications in subjects born during winter months has been shown to increase the risk for subsequent development of schizophrenia, even in patients genetically at risk,^{55–56} suggesting an interaction of environmental and genetic factors. In a review of studies employing the familial/sporadic distinction, Roy and Crowe⁵⁷ noted widespread methodological inadequacies across studies, but also that few differences were evident or replicated between familial and sporadic subgroups in the remaining methodologically rigorous studies.

The dimensional approach

The approaches described thus far can be broadly labelled as “categorical”: the grouping of subjects on the basis of the presence/absence of a diagnosis, symptom, or potential aetiological predictor. Numerous other categorical distinctions are possible, and evident within the literature, such as early/late age of onset, first episode/chronic illness duration, positive/negative symptoms. The categorical grouping of patients to provide more homogenous subtypes is in keeping with the tradition of the clinical subtyping of schizophrenia, initially proposed by Kraepelin (paranoid, hebephrenic, and catatonic forms). The dimensional approach represents a departure from this perspective, in conceptualising psychosis as groups of correlated symptoms (symptom dimensions) which can coexist in an individual patient, and may be present to a greater or lesser extent. The severity of individual symptoms will vary over time, but it is presumed that the correlational structure is robust. The dimensional model of psychosis aims to avoid the problems inherent in grouping individuals into mutually exclusive subtypes, which are consistently confounded by the combination of diagnostic categories, symptom types, or genetic/environmental influences, evident in the

typical clinical presentation. This approach has been fruitfully employed in, for example, the type I/type II model developed by Crow,⁵⁸⁻⁶⁰ and in the factor analytical approach reported by Liddle,⁶¹ identifying the three symptom dimensions labelled psychomotor poverty, reality distortion, and disorganisation. Furthermore, these symptom dimensions have been related to underlying biological processes, in terms of patterns of neuropsychological impairment⁶²⁻⁶⁴ and cerebral blood flow⁶⁵⁻⁶⁶ and anatomy.⁶⁷

Summary

There are thus at least four broad ways of initially defining our pathological groups in imaging research. The choice of any one particular definition of disorder ushers in a series of questions that may only be answered with respect to another definition. Does a pattern of brain activity that co-occurs with hallucinations truly reflect an hallucination or might it only occur in schizophrenic hallucinations? Does a pattern of imaging findings reflect a diagnostic entity or is it peculiar to a particular symptom profile? Does inconsistency within a diagnostic or symptom based grouping reflect state related psychological phenomena, or underlying aetiological differences, perhaps seen at the level of the genotype? Clearly, the difficulties are highly complex and will not be addressed by any single approach to experimental design but rather by the accumulation of data sets in which the correlations of brain activity with phenotypic and genotypic variables are examined. It has been possible, for example, to combine functional imaging with molecular genetics and developmental neurobiology. Egan *et al*⁶⁸ recently demonstrated that the *Val* allele of the catechol-O-methyltransferase (COMT) gene, is associated with both neuropsychological performance, and efficiency of prefrontal function. Moreover, they demonstrated increased transmission of the *Val* allele in schizophrenia. Such an approach, capitalising on the identification of specific genetic mutations and co-occurring behavioural deficits, may offer the precision that imaging studies require.

It is also important to acknowledge that the complexity of the huge multivariate datasets, generated by clinical functional imaging studies, is likely to demand powerful analytical approaches. Josin and Liddle⁶⁹ recently used a neural network to assign subjects to diagnostic categories after training of the network on positron emission tomography (PET) data. The success with which the network could carry out this task may indicate the value of such an approach as datasets grow ever larger and multistudy analyses are conducted.

CRITERION 2: HAS THE CHOSEN TASK ENABLED A CLEAR AND UNAMBIGUOUS MANIPULATION OF THE PSYCHOLOGICAL PROCESSES THAT WE WISH TO STUDY?

If a psychiatric illness reflects a brain dysfunction, then the possibility afforded by the newer functional imaging techniques, of exploring an indirect marker of brain function is most exciting. However, the possibility brings with it some intriguing difficulties, all based on the fact that a functional measurement is context specific—we cannot ignore the mental state that accompanied its measurement. At a broad level of distinction, one can group the use of imaging techniques, such as PET, single photon emission computed tomography (SPECT), and functional magnetic resonance imaging (fMRI), into studies which isolate the resting function of the brain, and those that employ a methodology involving cognitive “activation” (that is, a specific psychological state or occurrence is deemed to be active relative to some baseline state). We will consider these approaches in turn.

The major limitation with resting state studies is that the psychological processes involved are entirely underspecified as a measure of cortical physiology. It is also limited due to its variability across individual subjects.⁷⁰ Variations in rCBF

measures may therefore simply reflect the subjective experience of the procedure itself, rather than indicating underlying cerebral pathology. Andreasen *et al*¹⁸ also argue that the “resting state” is a misnomer:

“The brain does not become inactive or empty of thought in the absence of specific experimental tasks or instructions; on the contrary, patients report after scans that when at ‘rest’ they typically recalled past experiences, or made future plans.”

In addition, because resting state studies are usually associated with single measurements, they provide no clues about how a brain region may respond, in health or disease, to the challenge posed by a cognitive task.⁷¹ Berman⁷² points to an analogy in clinical medicine: cardiac stress tests provide greater information regarding cardiac function and reserve than do resting electrocardiograms. Berman thus considers a cognitive activation study to be a “cortical stress test” in so far as it imposes a selective physiological load on a cortical area of interest.” Berman’s analogy is particularly pertinent in reference to several studies which have reported that functional abnormalities evident during the performance of cognitive tasks were not found during resting baseline rCBF.⁷⁰⁻⁷³⁻⁷⁴ Thus, as Gur and Gur⁷⁵ suggest, the “cortical stress test” may be critical in establishing the link between the behavioural deficits evident in psychosis, and the responsiveness of the brain as a function of task related demand.

In the light of such issues, many functional imaging studies involve determination of brain activity while the subject is engaged in a specific mental task. This task is considered to be compounded of psychological subprocesses, and the brain activity that accompanies it is assumed to reflect the neuronal instantiation of these processes. Carefully considered task manipulations are assumed to decompose these processes. Thus, if task 1 involves processes A and B, and task 2 only involves process B, the subtraction of activity levels associated with each task should leave us with a set of brain regions that reflect the neuronal accompaniment to process A. The same logic holds if we are referring to symptoms rather than processes. Of course, a fundamental assumption in this approach, and one that often requires further examination, is that we are measuring brain activity in association with a process or phenomenon that actually exists. This assumption concerns the idea that mental states can be fractionated in a particular way and that this fractionation will be evident at the level of brain anatomy and physiology. Because this is a central tenet driving cognitive activation studies then it follows that such studies are always dependent upon the validity of a particular psychological model (whether it is a model of function or dysfunction).

This comparison of pairs or sets of tasks, the “cognitive subtraction” approach, relies upon the assumption that an experimental manipulation of task demands enables us to insert or remove cognitive processes and it is therefore utterly dependent on a clear understanding of the cognitive components of all of the tasks used. Moreover, as we shall discuss in the next section, it must be remembered that apparently similar task demands, when made of a patient group, may not engage the same components. This assumption must be made irrespective of whether a simple pairwise (activation task versus control task) design is used or a more subtle manipulation of task demand across a series of conditions (the so-called parametric design) is used.

Although parametric task manipulation has been successfully used as a way to examine the profile of brain response to increasing tasks demands⁷⁶⁻⁸² in a way that has not been possible with simpler cognitive subtraction experiments, it must be remembered that an apparently linear increase in task demands may be associated with responses that are non-linear. Thus, increasing cognitive load may not always

represent a purely quantitative change across the various parameter levels, but may also invoke a qualitative change in the requirements of the task.⁸³

Moreover, both pairwise and parametric task designs require the same assumptions, one of which centres around the notion of “pure insertion”—that is, that the phenomenon of interest can be identified or manipulated in isolation from other brain processes. This assumption is by no means a safe one.^{84–85} Indeed, it seems highly likely that certain cognitive processes may be highly correlated. Thus, for example, a task that purports to introduce a particular cognitive process may inadvertently require greater attentional resources and the selection of performance optimising strategies. This challenges the central assumption governing cognitive subtraction designs, routinely used in functional imaging experiments. This critique is equally applicable to psychopathological processes: to identify the neuronal correlates of an obsessive rumination, one might make a series of measurements while the subject experiences such a rumination and compare regional levels of activity with measurements made in a control task that was identical to the obsessive state in every possible way apart from the absence of the rumination. Is it really plausible that a phenomenon like this can be “inserted” into the mind without having a drastic effect upon other mental processes (attention, memory, speech etc)?

It is possible to design experiments that specifically address or obviate the need to assume that we can isolate and manipulate the cognitive processes of interest across tasks. One approach is to explore how brain processes interact with each other using factorially designed experiments.^{86–87} Thus process 1 may be influenced by whether or not process 2 is engaged at the same time. The only way to determine whether this is so is to explore brain activations associated with process 1 in both the presence and absence of process 2. Such experimental designs relieve, to some extent, the assumptions of pure insertion. They do not, however, magically account for all possible interactions of processes, only those which are specifically taken into account by the design and analysis. Another approach has been to use multiple tasks and analyses and to search for the common activations that theoretically reflect a single common process, referred to as a conjunction analysis.^{86–87} Such an approach accepts that single comparisons may be adulterated by interactions of processes but aims to isolate the purer aspects of the process by concentrating only on those commonalities that prevail across different tasks, different baselines, and different contexts.

Summary

There are thus several approaches which can be adopted in constructing experimental designs in functional imaging studies, with advantages and disadvantages to each. The appropriate design will depend on the nature of the particular function (or dysfunction) of interest. One approach which is becoming increasingly employed in fMRI studies is the use of event related designs which provides the capability to randomise trial types during scanning—an approach commonly used in neuropsychological and electrophysiological studies. Conventional block designs in fMRI and PET group related stimuli into epochs, presented in a periodic design. This grouping, and the associated averaging of the time-series over several epochs has several limitations^{88–89}: (1) the repeated presentation of similar stimuli may lead to habituation, automatism, or fatigue; (2) if the pattern of experimental blocks is predictable, this may lead to anticipation and/or prediction of subsequent stimuli; (3) the blocked design is insensitive to the temporal development of the functional response to individual trial types. Event related designs circumvent such problems, and additionally, offer the opportunity to select trial types post hoc. Some studies have begun to exploit these advantages of event related fMRI, accessing aspects of cognitive function not previously amenable to investigation using

blocked designs—for example, identifying the role of the anterior cingulate in error monitoring,^{90–92} dissecting the sub-components of memory related processes,^{93–94} and novel target detection.⁹⁵

The application of event related imaging to studies of abnormal function in psychiatry also offers specific advantages; for example, the capability to exclude trials on a post hoc basis for which the subject responded incorrectly, in order to match task performance in cognitively impaired psychiatric patients to control groups. Event related functional imaging also facilitates the investigation of the fleeting symptoms and experiences of psychiatric patients, such as tics in Tourette’s syndrome,⁹⁶ or cognitive dysfunctions considered central to the illness, but not amenable to blocked designs, such as odd-ball recognition^{97–98} and error related internal monitoring.⁹⁹

Event related designs are therefore an important breakthrough in the experimental approaches available in neuroimaging, and will likely become increasingly evident in the literature. The reduced signal to noise inherent in this approach however means that this will complement rather than replace other strategies currently available.

CRITERION 3: RELATING PHYSIOLOGY TO DISORDER—HOW MAY WE INTERPRET CHANGES IN BRAIN ACTIVATIONS IN THE PATIENT GROUP?

Assumptions made in mapping normal and abnormal cognitive processes

Although a functional imaging experiment is essentially a simple exploration of the relation between an independent and a dependent variable, we must nevertheless acknowledge that, as the independent variable in neuropsychiatric research is a mental state, it is almost invariably underspecified. In the cognitive domains that are of direct relevance to psychiatry—language, memory, attention—the cognitive models that inform our task design are incomplete. The success with which a functional neuroimaging study can disentangle the cognitive processes comprising specific mental states, can explore those processes in the setting of abnormal mental states, and can establish the relevance of these observations to various disease processes, will be dependent upon the answers to certain key questions. These are detailed in the sections that follow.

Can psychopathological processes be adequately mapped onto specialised brain regions?

Debates continue over whether both normal and abnormal function may best be characterised according to separable cognitive modules or an integrated and even equipotential system. Functional imaging, as it has been most often used, assumes a segregationist perspective, aiming to map function onto discrete regional anatomy. In many cases this may be a reasonable assumption, but it must be borne in mind that a full description of psychological processes in neuronal terms is likely to demand an appreciation of interregional integration. There is evidence that psychopathological processes are explicable in terms of impaired integration rather than a localised abnormality of any one region. Similarly, cognitive models of psychotic symptoms emphasise a failure of integration of cognitive processes, rather than a single deficit.¹⁰⁰ Structural imaging has also suggested that volumetric deficits in schizophrenia may be best characterised by abnormal connectivity,^{101–102} which may be neurodevelopmental in origin.^{103–104} The whole brain coverage afforded by PET and fMRI make it possible to consider the entire system rather than focusing on single regions in isolation. Functional imaging studies have already provided an indication of dysconnectivity in schizophrenia: Frith *et al*⁷¹ and Fletcher *et al*¹⁰⁵ found that prefrontal activation in healthy volunteers was associated with concomitant temporal deactivation. Although patients

showed normal prefrontal task activation, the negative correlation between prefrontal and temporal regions was absent. These studies provided the first indication of abnormal frontotemporal connectivity in schizophrenia using functional neuroimaging. However, some later studies have failed to replicate these findings in those affected by, or at genetic risk of schizophrenia¹⁰⁶ or bipolar disorder.¹⁰⁷ The introduction of path analysis to imaging data facilitated empirical modelling of causal interactions and has provided further support for the disconnection hypothesis of schizophrenia.¹⁰⁸ Thus there is now considerable evidence accumulating that schizophrenia in particular, but probably also other conditions, such as Alzheimer's disease,¹⁰⁹ may be understood in terms of a disorder of functional integration in the brain, which must be reflected in the analysis and interpretation of functional imaging data.

Is the psychopathological phenomenon amenable to activation study methodology?

For a phenomenon to be studied in a single subject, its severity must fluctuate across scanning measurements. Thus, we must make all of the assumptions about whether a phenomenon may be identified, isolated, and manipulated as discussed above. The fluctuation of the phenomenon can occur in terms of the intensity with which it is experienced (for example, the "amount" of phobic anxiety that is felt) or in a dichotomous way (for example, an auditory hallucination that is present during some measurements or absent during others). Reliable measures for the onset or offset of the phenomenon of interest and/or some clear and plausible scale for rating its intensity are crucial. As such, symptoms are often rather imprecise in all of these parameters, this is a difficult challenge. In addition, certain types of phenomena, by their nature, resist this type of experimental design. A delusion for example is both very difficult to rate in terms of strength or severity but also may fluctuate in its intensity over long periods but not over the course of a single scanning session.

Is the observation of a specific pattern of brain activity in association with a particular phenomenon interpretable in terms of abnormal underlying processes?

This issue really surrounds our understanding of psychopathology in terms of a disruption in underlying cognitive processes. Simply mapping a particular type of psychopathology without the attempt to develop it more fully in terms of a testable cognitive model would be a rather unambitious application of the techniques. It is difficult to imagine the ultimate usefulness of identifying a "hallucinations centre" or an "anxiety area" unless these pointed directly to a structural brain pathology (see below). Rather our goal is to generate models of psychological function and to express these in terms of patterns of brain activity. To understand abnormal patterns of brain activity we must have hypotheses about how the psychological processes are disrupted.

Does the observation of a specific pattern of brain activity in association with a particular phenomenon carry information about the underlying disease?

Consider a study in which we had satisfied ourselves that we had identified the neuronal activation associated with auditory hallucinations in a group of schizophrenic patients. Suppose that we have a control group who have no experience of mental illness generally and no experience of auditory hallucinations specifically. An analysis of imaging data within the patient group has told us about the brain regions that are active during hallucinations. The next question concerns whether these findings tell us anything about schizophrenia. Clearly, comparison with a control group does not address this issue as we have no idea of the neuronal correlates of auditory

hallucinations in control subjects and therefore the two groups are distinguished both by the disease and by the psychopathological feature. On this basis alone, we cannot disentangle the relative effects of these two factors. Instead we would need to find a non-schizophrenic group of patients with (descriptively identical) auditory hallucinations. Perhaps any differences between these two groups would be disease specific. This would hold only if we were convinced that the psychopathology was comparable across the two groups. The question of how we would ensure this in order to justify our assumption is a highly complex one.

Is the functional capacity to respond to increasing cognitive challenge equivalent across diagnostic groupings? Is it affected homogeneously within diagnostic groups?

Numerous studies have employed a parametric manipulation of cognitive processes, typically memory tasks, to investigate the neurophysiological response to increasing cognitive demand. Callicott *et al*¹¹⁰ demonstrated that the prefrontal cortex produces an "inverted U" response to increased cognitive load, presumed to represent the capacity constraint of working memory. But how does the brain respond to increasing demand in psychotic patients? Manoach *et al*¹¹¹ and Callicott *et al*¹¹² found increased prefrontal response to a working memory task in patients with schizophrenia, in comparison with controls. However, Manoach *et al* noted a negative correlation between error rate and prefrontal activation in the patients, suggesting that prefrontal activation increases with demand, until cognitive capacity is exceeded. As they noted, this leads to the intriguing speculation that further increases in load may have resulted in a hypofrontal response in the patients, whereas this increase may have remained within the performance capacity of the controls, and therefore resulted in *increased* activation in line with demand, thus reversing the between group comparison they found at lower cognitive loads. Callicott *et al* noted that this increased response in patients to a working memory task was predicted by reduced N-acetylaspartate (NAA) concentrations in dorsolateral prefrontal cortex, supporting the assumption of the relation to neuronal pathology.

These findings are congruent with the capacity model of cortical function proposed by Just *et al*.^{113 114} Briefly, this model suggests that different cognitive tasks may compete for common, capacity limited neural resources. As the demands on processing resources increase, there is increasing functional activation of the brain regions specialised to perform the relevant tasks until a capacity limit is reached, at which point activation by one or more of the competing tasks is attenuated. In extending this model to psychopathology, response capacity may be subsumed by exogenous, task related activity, but in addition, endogenous, pathological activity, which may compete for capacity constrained physiological resources. For example, "resting" brain activity in patients experiencing auditory hallucinations is associated with a regionally specific increase in endogenous activity of the superior temporal and inferior frontal cortex and supplementary motor area (SMA).^{46 115} The capacity model predicts attenuated task related activation of these regions due to competition for overlapping neural resources. This is supported by findings of reduced activation of frontal and temporal regions in response to a verbal self monitoring task,¹¹⁶ and reduced activation of the auditory cortex in response to external auditory stimulation¹¹⁷ in patients with a history of auditory hallucinations. This relation between available capacity and functional response has also been found in healthy volunteers: Kastrup *et al*¹¹⁸ reported a negative correlation between focal activation during visual stimulation and baseline rCBF.

In patients with psychosis, the interpretation of regional deficits from functional imaging experiments will therefore be

determined only by careful consideration of the cognitive limitations imposed by the illness, and the physiological constraints imposed by pathological competition for limited neural resources. These effects would be expected to vary across individual patients according to symptomatology, and dynamically in relation to the course of the illness.

Are psychopharmacological and psychopathological effects identifiable and dissociable?

A fundamental consideration in any functional imaging study involving psychiatric patients is the potentially confounding effect of antipsychotic medication. Administration of neuroleptic drugs is associated with increased metabolism in the basal ganglia.^{31 41 119–127} Pharmacological manipulations which serve to increase dopaminergic transmission in the prefrontal cortex, including administration of pibridel,²⁴ apomorphine,¹²⁸ amphetamine,¹²⁹ and risperidone¹³⁰ have been shown to increase prefrontal activation during cognitive activation in patients with schizophrenia.

However, the potentially confounding effects of pharmacotherapeutic interventions are often overlooked in experimental designs involving psychiatric patients. In such circumstances it is simply not possible to dissociate the effects of illness and treatment in the interpretation of any observed group differences. This is particularly problematic in functional imaging studies, in which drug treatment may affect outcome measures on several levels:

(1) *psychological*: antipsychotic drugs may induce cognitive impairment, or exacerbate existing deficits associated with the illness.¹³¹

(2) *neural*: electrophysiological studies have demonstrated direct effects of anti-psychotic drugs on the regulation of neuronal firing.¹³²

(3) *neurovascular*: dopaminergic terminals form synapses in close proximity to the cerebral vasculature and dopamine agonists have been shown to cause vasoconstriction¹³³ and a global reduction in cerebral perfusion.¹³⁴ Careful experimental design is therefore required to precisely determine and delineate the effects of disease and its treatment.

CONCLUSIONS AND SUGGESTIONS FOR FUTURE RESEARCH

In drawing together some of the conceptual considerations in the application of functional imaging to psychiatric conditions, we have aimed to identify specific issues and challenges which remain to be resolved in the field. However, such considerations should be viewed in context: it should be emphasised that the use of functional imaging offers a remarkable opportunity to study the functional architecture of the living human brain. This technique may lead to paradigmatic changes within psychiatry, challenging current concepts and assumptions, and suggesting new models of psychosis. The application of this technique to psychiatry is a relatively recent development. The unresolved questions articulated in this article concerning precisely how this technology should be applied, and how the observations with which it provides us are to be interpreted, should be seen only as a reflection of the early stages of the scientific community's understanding and application of a profoundly important tool in cognitive neuroscience.

The broad implication of this review is that the fulfilment of the potential of functional imaging to contribute to an understanding of the neurobiological basis of psychiatric disorders is critically dependent on parallel advances in our ability to precisely identify the clinical population of interest, and the degree to which the assumptions underlying our measurement of human brain function can be validated and related to pathophysiological mechanisms. So how is psychiatric imaging to address these related issues? Research efforts implicitly

accepting the current psychiatric taxonomy are forced to confront numerous confounds, the effect of which can be considerable on functional imaging indices, or indeed any other measure. Laws *et al*¹³⁵ suggest that a more "theoretically determined" approach may be to adopt the case study design, in conjunction with group studies: "Single case studies (alongside group studies) may provide a method that can both accommodate and exploit the heterogeneous character of schizophrenia that has, for so long, dogged research into this disorder." David¹³⁵ advocates the identification of "a single 'ideal' case with one of these 'pure' deficits which can become the lynch-pin of theoretical development. Better still is the identification of a pair of cases where one has lost function X but has normal function Y, and the other has the opposite pattern of abilities/disabilities, the magic double dissociation." Current imaging technology provides the capability to produce reliable measurement of brain activation in single subjects, thus the case study approach may become increasingly important in future brain imaging research. This further suggests the possibility of clinical application in the medium term, such as differential diagnosis, and predicting treatment response or developmental trajectory. However, the ultimate success of functional imaging in contributing to clinical psychiatric practice will depend, not only on the ability to visualise (possibly abnormal) brain function in a single individual, but also on a vastly improved understanding of normal variability of human brain structure and function in the general population. A major future research priority for imagers interested in clinical applications is therefore a large scale, epidemiologically based engagement with endophenotypic variability of the human brain over the course of the life cycle.

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