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Scanning Patients With Tasks They Can Perform

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Abstract: We present an overview of the types of imaging experiments that can be performed on psychologically impaired patients. The critical observation from such studies is a differential pattern of activation in the patients and normals. Underactivity is interpretable only when the patients make normal responses. In this context, a failure to activate a component region of the normal system implies that this region was not necessary for task performance. Overactivity indicates either cognitive or neuronal reorganisation. Neuronal reorganisation is indicated only if the patient performs the task using the same set of cognitive operations as normal subjects. Cognitive reorganisation can be demonstrated if the same activation pattern is elicited by normals when they are co-erced into using the same cognitive implementation as the patient. We conclude that the interpretation of neuroimaging studies of psychologically impaired patients depends on intact task performance and a detailed task analysis. When these criteria are met, patient studies can be used to identify: (1) necessary and sufficient brain systems, (2) dysfunction at sites distant to damage, (3) peri-damage activation, and (4) compensation either at a neuronal level when pre-existing cognitive strategies are re-instantiated using duplicated neuronal systems (degeneracy), or at a cognitive level when alternative cognitive strategies (and their corresponding brain systems) are adopted. *Hum. Brain Mapping 8:102–108, 1999.*

Key words: cognitive level; task performance; neuroimaging

INTRODUCTION

A report entitled ''Scanning patients with tasks they can perform'' may appear simplistic. The point is, given the opportunity to perform a functional neuroimaging experiment on a patient with a selective cognitive deficit, the first experiment that usually springs to mind for a neuropsychologist is one that investigates the abnormal neural processing underlying the observed deficit. This could be called ''dysfunctional neuro-imaging.'' However, if a patient cannot perform the task, the corresponding neuronal system cannot be activated, and it is not possible to tell whether the abnormal neural processing is a consequence of the performance deficit or whether the performance deficit is a consequence of the abnormal neural processing [see Fletcher et al., 1998]. The simple consequence is that functional imaging studies of patients need to be designed around tasks the patient can perform.

Here, we present a selection of the types of functional neuroimaging studies that can be conducted on neurologically damaged patients (summarised in Table I). We start with the premise that a patient must be able to perform the activation task, at least to the extent that the explicit task instructions are adhered to and appropriate responses are made. Two types of patients can then be distinguished: those who perform the task using the same cognitive and neuronal architectures as normals and those who show an abnormal cognitive or neuronal implementation.

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TABLE I. How patient activations can contribute to normal and abnormal models of processing

Patient activations	Interpretations for: Patients	Normals
Normal:	Recovery to normal	—
Abnormal:		
1. Patients not normals:	(a) Neuronal change	Duplicate system
	(b) Cognitive change	Alternative system
2. Normals, not patient		
(a) In lesion only:	—	Redundancy
(b) Distant to lesion:	Dys-integration	Connections
3. Correlation changes:	Disconnection	—

NORMAL COGNITIVE AND NEURONAL ARCHITECTURES

Patients who appear to perform a task using the same cognitive and neuronal architecture as normals are interesting only when it is unpredicted, e.g., when structural imaging (with CT or MRI) indicates damage to a neuronal system thought to be important for the task, and functional imaging indicates that the area in or around the lesion is still responsive [see Warburton et al., 1999]. Functional imaging has an important role to play in evaluating the extent to which ''peri-damage'' activation contributes to recovery of function. However, for the purposes of this report, we focus on functional imaging studies of patients who retain the ability to perform a task but respond abnormally either at a cognitive or neuronal level.

ABNORMAL COGNITIVE OR NEURONAL ARCHITECTURES

Abnormal task implementation, in the context of appropriate responses, can be inferred either a priori from behavioural data, or directly from the imaging data.

Abnormal behaviour

Abnormal task implementation is indicated by behavioural measures such as reduced accuracy or delayed response times relative to normal. In the case of reduced accuracy, the analysis of functional imaging data needs to model correct responses separately from incorrect responses (i.e., an event-related design is required). Patients can then be compared to normal on trials (or blocks of trials) when performance is matched. Another approach to discounting performance differences is to enter normal and patient response measures (e.g., reaction times) into the analysis as confounds.

Behavioural assessment may also reveal explicit signs that an abnormal cognitive strategy is being used. For example, some patients may retain the ability to read words but name the letters of the word before producing a response, a so-called letter by letter reading strategy. If we know apriori that the patient is using an abnormal set of cognitive processes to perform a task, then functional imaging can specify the corresponding neuronal systems. Knowing which areas of the brain are important for alternative cognitive strategies may be useful for diagnosing whether other patients adopt these strategies and designing cognitive rehabilitation programs. For instance, it may not be effective to attempt to teach a patient a particular cognitive strategy if the necessary neural systems underlying that strategy are damaged.

Abnormal activations

Even when behaviour appears normal, functional imaging can reveal abnormalities in terms of different activation patterns in the patient and normals. Below (and in Table I), different types of abnormal activation are classified into three types: when regions are activated in (A) patients more than normals, (B) normals more than patients, and (C) both patients and normals, but with different correlations among regional responses (i.e., changes in functional connectivity). The types of conclusions that can be drawn from these different profiles are discussed below.

First, we discuss the causes of differential activation, summarised in Figure 1. Differential activation, in the context of normal behavioural responses, implies a change in cognitive or neuronal implementation. Changes in cognitive implementation occur when a

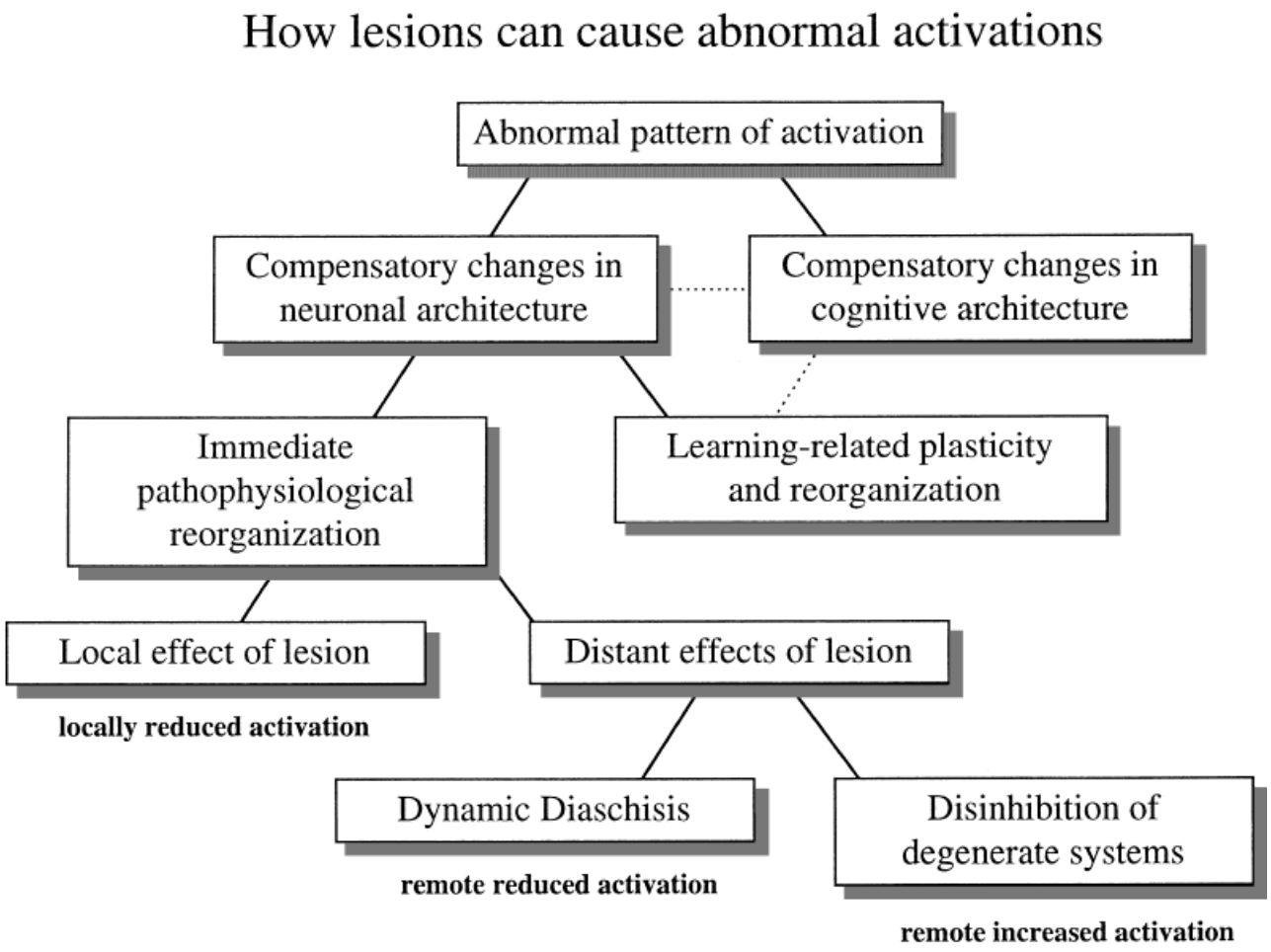

Figure 1.

patient uses a different set of cognitive processes either because a new cognitive procedure has been learned, or because of increased demands on normal processes, particularly attention. Changes in neuronal implementation are mediated by changes in the strength of pre-existing connections.[1] This does not necessarily entail learning-dependent plasticity. For instance, abnormal activation may be simply a direct consequence of brain damage that can disrupt neuronal responses at, or distant to, the lesion site. Abnormal responses distant to the lesion site suggest the dysfunctional region has been disconnected from its normal inputs. This disconnection may result in *overactivity,* due to disinhibition (reduced glutaminergic drive to inhibitory interneurons) of a duplicate system, or *underactivity* (i.e., a diaschisis).

[1]In the mature brain, rewiring does not occur because neuronal systems and extrinsic connections are fully established.

Overactivity: regions where patients activate more than normals. Overactivity can be observed either when patients activate "new regions" that are not activated by normals, or when activation in a normal region is enhanced. The latter can be ascribed to disinhibition at a neuronal level, or increased demands on the cognitive processes implemented in the affected region, at a cognitive level. New regions are more difficult to interpret. One possibility is that the abnormal activation pattern represents a change in cognitive strategy; the other is that there has been a change in neuronal implementation. This may entail learning related long-term changes in synaptic efficacy, or it may involve rapid reorganisation following deafferentation [Buonomano and Merzenich, 1998] that reflects a disinhibitory phenomenon. For instance, neuronal systems for a particular cognitive process may be duplicated in the normal brain with the dominant system inhibiting the others. When the prepotent

system is damaged, the less dominant systems are able to respond. The duplication of functionality in neuronal systems has been referred to as "degeneracy" [see Edelman, 1989]. This property renders a function immune from the effects of focal damage. Furthermore, because functionality is preserved, the effect of damage may never be detected by neuropsychological assessment. Functional imaging studies of patients, therefore, have an important role to play in the identification of degeneracy—the multiplicity of sufficient brain systems for a cognitive function.

However, before conclusions regarding neuronal changes can be reached, changes in cognitive implementation must be excluded. This is not possible from just the functional imaging data that depends on neurophysiological responses. The cognitive components of a task need to be specified apriori from behavioural data and the task analysis (i.e., the decomposition of a task into the componential cognitive and sensorimotor processes it comprises). However, a task analysis is never as refined or as comprehensive as one would like because there are certain attributes of cognitive processing (e.g., attention, implicit processing, and habituation) that are not always amenable to measurement, and these subtle cognitive differences may cause changes in neuronal implementation. The critical point to be made here is that the cognitive level of description of a task needs to be as detailed as possible in order to conclude that the patient is using the same cognitive architecture as normals, and any changes at the neuronal level are due to neuronal rather than cognitive reorganisation. The more detailed the task analysis, the more valid the inferences about changes in neuronal implementation.

Just as inferences regarding neuronal reorganisation depend on excluding an explanation in terms of cognitive reorganisation, inferences about cognitive reorganisation depend on excluding explanations in terms of neuronal reorganisation. This might be achieved with neuroimaging if the same neuronal systems activate when normal subjects adopt the same strategy as the patient. For example, to confirm that the differential pattern of activation seen in a dyslexic patient relates to a letter by letter reading strategy, the equivalent activation pattern needs to be elicited in normals when they also read letter by letter. To our knowledge, this experimental technique has not yet been explored. As our understanding of normal neuronal systems expands, we should be able to identify the patients' strategy from the neuronal responses. This would entail associating the regions activated by the patient to the cognitive processes that normally produce the same response. In summary, changes in neuronal responses may result from cognitive or neuronal reorganisation. It is only possible to make inferences about one level of reorganisation when the other can be shown to be unaffected.

Underactivity: regions where patients activate less than normals. Underactivity can be observed either when patients fail to activate a region consistently activated in normals or when activation in a normal region is reduced. A complete failure to activate a normal region, despite normal task responses and the absence of overactivity in other neuronal systems, indicates that the dysfunctional region was not necessary for task performance. This has important implications for normal functional anatomy. By systematically studying patients, who retain the ability to perform a task despite lesions to different parts of a neuronal system, functional imaging can delineate the necessary and sufficient brain system (i.e., identify a sufficient set of regions that can meet the task requirements). This approach requires both neuropsychological and neuroimaging investigations. Neuroimaging in normal subjects identifies a set of distributed regions. Neuropsychological assessment, on patients with damage to components of the normal system, distinguish lesions that result in performance deficit (i.e., regions necessary for performance) and lesions that do not result in performance deficits. Neuroimaging of the patients with no performance deficit is then required to confirm that task performance is not maintained by peri-damage activity or a change in neuronal implementation. A sufficient set of regions then comprises all regions activated by normal subjects minus those that are not necessary in each patient (see Fig. 2). Note that, again, the only useful results here obtain from scanning patients with tasks they can perform. The other important point is that there may be "degenerate" sets of sufficient regions that render no region necessary.

An example of how imaging studies of patients can delineate the necessary and sufficient components of a neuronal system is given by two studies of different patients performing a semantic decision task (see Fig. 2). In one study, the patient had a large left fronto-parietal lesion; in the other, the patients had extensive damage to the anterior temporal lobes. All patients retained the ability to perform semantic judgments within the range of normal subjects. Functional imaging of the patient with the large fronto-parietal lesion [Price et al., 1999] demonstrated that he activated left temporo-parietal regions normally, but that there was no activation in the left inferior frontal lobe (seen consistently in 12 normal subjects) and no activation in the right inferior frontal cortex that might have been

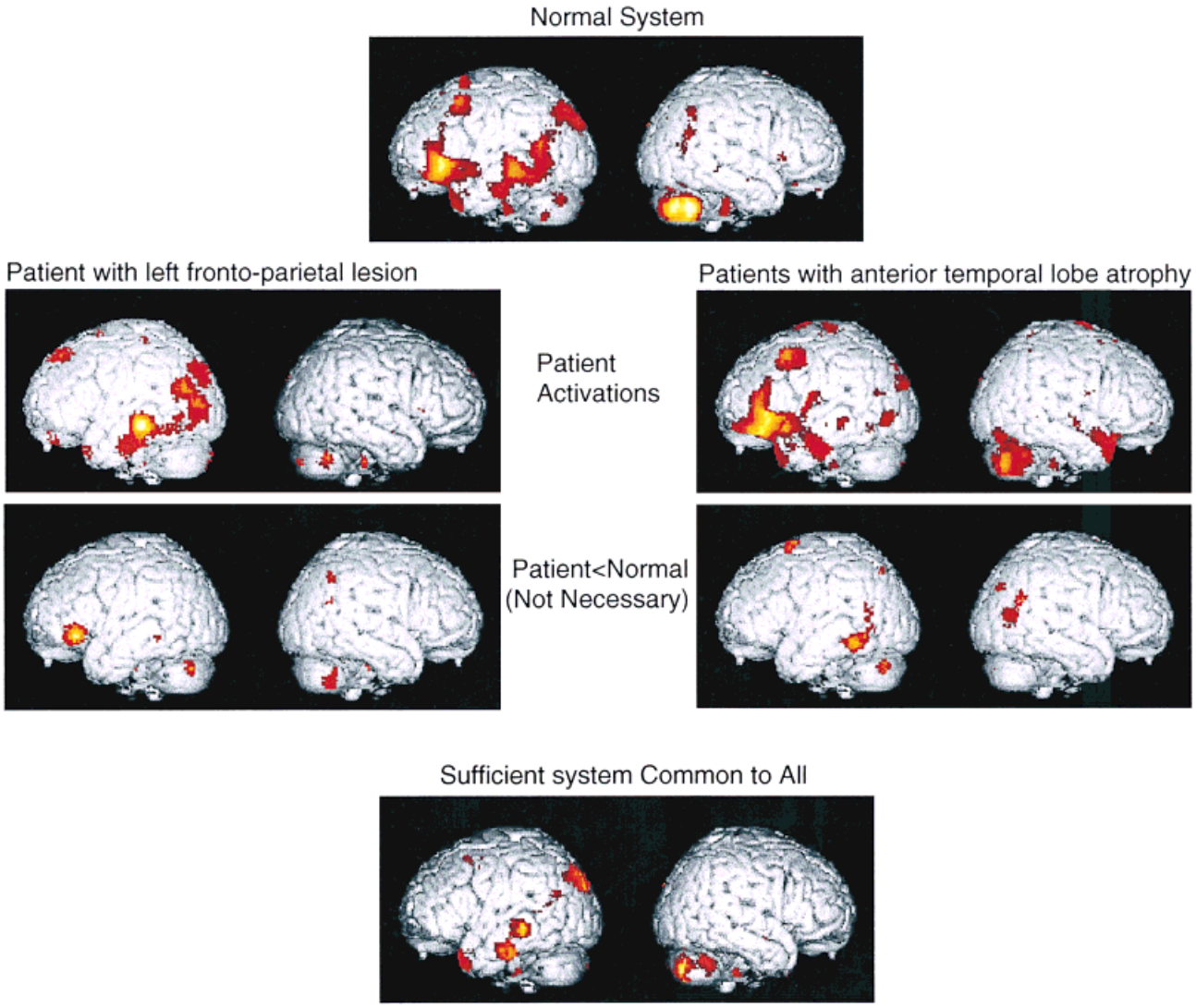

Figure 2.

associated with neuronal reorganisation. These results suggest that the left inferior frontal cortex is not necessary for intact performance on semantic decisions. A contrasting pattern of activation was observed in four semantic dementia patients who all had atrophy in a ventral left anterior temporal region usually activated during semantic decisions [Mummery et al., 1999]. These patients activated all regions of the semantic network, including the damaged left anterior temporal cortex but excluding the left posterior inferior temporal cortex that did not appear to be damaged in structural scans. Thus in one study, the semantic decision task was performed without activation of the left inferior frontal cortex, and in the other study, the same task was performed without activation of the left posterior inferior temporal lobe. From this we might conclude that activation in the left inferior frontal and the left posterior inferior temporal cortex was not necessary for the task. It is possible to hypothesize that intact task performance might be possible following damage to any subcomponent of a system. An analogy might be that it doesn't matter which finger you chop off, the remaining fingers are able to adapt to some task requirements. This would be a case of degeneracy (see above). However, in the above example, lesion studies indicate that impairments on semantic tasks do result from extensive damage to the anterior temporal cortices [Hodges et al., 1992] and in patients with transcortical motor aphasia who have damage to the left inferior temporal and posterior inferior parietal cortices, the left thalamus, and the white matter connecting these regions [Alexander et al., 1989]. In short, lesion

studies are required to identify the necessary regions and functional imaging studies on normals and patients are required to identify the sufficient sets of regions (that may or may not be degenerate).

The area that fails to activate in the patients can either be at the site of lesion, as in the case of the patient with the damaged left frontal cortex, or distant to the lesion, as in the case with the semantic dementia patients. In the latter case, the dysfunctional, undamaged region must have been disconnected from the site of damage. A disconnected undamaged region is either rendered abnormally responsive in all contexts, or it may function normally when it does not rely on inputs from the damaged region. The occurrence of normal activation in some contexts, but dysfunctional responses when integration with the damaged region is involved, has recently been illustrated in a patient with an extensive left frontal lesion (Price, Warburton, Friston, submitted). This phenomena has been referred to as ''dynamic diaschisis.'' In a semantic paradigm that relied on temporo-parietal interactions, the patient showed normal activation of the undamaged left posterior inferior temporal cortex, but during a reading paradigm (which normally activates the left inferior frontal cortex and the left middle and posterior temporal cortex), the left posterior inferior temporal cortex responded abnormally (decreased activity rather than increased activity). These results suggest that the left posterior inferior temporal cortex responds abnormally only when it depends on input from the damaged frontal region (as in the reading paradigm).

In summary, patients can maintain the ability to perform a task, yet fail to activate the full set of regions associated with normal task performance. This might be predicted when the failure to activate is at the lesion site, as in the case of the patient with the left frontal lesion. More interestingly, a failure to activate may occur distant to the lesion site (as in the case of the patients with semantic dementia), and this can only be revealed with functional imaging. The systems level approach that neuroimaging offers, therefore, has a vital role to play in identifying dysfunction in undamaged regions. In addition, although conclusions regarding the necessity of an activated region only can be made using the lesion deficit model, functional neuroimaging is required to make conclusions that a region is ''not necessary'' by eliminating the possibility that the patient has compensated for the damage by activating either peri-damage tissue or other areas that are not usually engaged by normals. By combining lesion and imaging studies, the necessary and sufficient systems can be identified (see Fig. 2).

Abnormal correlations between regions

In patients with neurological damage following a specific insult, the aetiology of abnormal responses is known. However, this is not necessarily the case when structural imaging provides no indication of focal pathological damage, e.g., in schizophrenia. In this case, functional imaging studies of abnormal functional integration can be useful. Such studies use measurements of the functional connectivity among regions. Essentially these measurements are based on temporal correlations between activity in distant cortical regions. In electrophysiological studies, which record spike trains of neural activity, the temporal scale is in the order of milliseconds. In functional neuroimaging, which records hemodynamic changes, the temporal scale is in the order of seconds and a significant correlation simply implies that activity (pooled over the time scale) goes up and down together in distant regions. Temporal correlations imply functional connectivity that can be mediated in two different ways: from direct monosynaptic or indirect polysynaptic connections between the correlated regions (i.e., activity changes in one region cause activity changes in another), or from independent connections to another region that is the shared source of correlated activity (the ''common input'' scenario). This distinction illustrates that temporal correlations do not necessarily imply either direct or indirect connections between correlated regions.

Studies of functional connectivity in schizophrenia have shown that there are abnormal correlations between activity in the prefrontal and temporal regions during word generation tasks [see Friston and Frith, 1995]. More specifically, in normal subjects activity in bilateral superior temporal cortices during word generation (relative to word repetition) is negatively correlated with activity in the prefrontal cortex, but in three different groups of patients with schizophrenia, activity in the left superior temporal cortex was positively correlated with prefrontal activity. This pattern of reversed coupling is very similar to the abnormal temporal responses described above in the patient demonstrating dynamic diaschisis. However, in the case of schizophrenia, the abnormal coupling cannot be ascribed to a lesion in the remote source of afferents (e.g., the frontal lobe), but is due to a more subtle pathophysiology that may involve the connections themselves. As noted above, abnormal correlations can result directly from connections between the frontal and temporal regions, or indirectly via shared influences from a third region. One hypothesis [Dolan et al., 1995; Fletcher et al., 1999] attributes the abnormal

fronto-temporal integration in schizophrenia to abnormal modulation from the anterior cingulate. This hypothesis could be tested with studies of effective connectivity [Friston et al., 1997].

CONCLUSIONS

Functional imaging studies of patients who retain intact task performance can inform both normal and abnormal models of processing because they provide important measurements that are not available from lesion or behavioural data: evidence for peri-damage activation, dysfunction in regions distant to the site of damage, and degeneracy. With respect to normal models, functional imaging studies of patients can be used to identify necessary and sufficient brain systems and degenerate sets of sufficient brain regions that can be called upon in the service of a task. Functional imaging studies of patients can also contribute to normal models by indicating functional integration between regions. For instance, the study of the patient who showed abnormal responses in the left posterior inferior temporal cortex following damage to the left frontal cortex indicated functional integration between these two regions. With respect to models of abnormal neuronal processing, we have distinguished between changes in cognitive and neuronal implementation. Changes in cognitive implementation could be inferred if normal subjects show similar activations when co-erced to adopt the same strategy. Changes in neuronal implementation are more difficult to isolate and depend upon task analysis and behavioural evidence that the patients and normals are performing the task with the same cognitive architecture. Changes in neuronal implementation can involve ''disinhibition'' phenomena, or learning related plasticity underpinning the recovery of a lost cognitive function. It is likely that many future studies, combining neuropsychological assessments and imaging data from both normal and patient populations, are required before imaging can be used to facilitate rehabilitation.

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