PHILOSOPHICAL TRANSACTIONS OF THE ROYAL SOCIETY B BIOLOGICAL SCIENCES

General Discussion

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GENERAL DISCUSSION

T. W. Robbins (*Department of Experimental Psychology, University of Cambridge, Downing Street, Cambridge CB2 3EB, U.K.*). I am not completely clear about the theoretical status of deactivation. In what circumstances is it an artefact of the data analysis and in what circumstances is it a real effect? In the case of it being a real effect then I would like to ask about the theoretical implications of deactivation particularly with respect to different areas within the prefrontal cortex. We have seen increases in activity in dorsolateral prefrontal cortex in association with corresponding reductions in activity within medial prefrontal cortex in the context of the Tower of London task (Baker *et al.* 1996). We have also heard from Danny Weinberger that the impaired performance of schizophrenics on the WCST is associated with a reduction in activity in dorsolateral prefrontal cortex along with a corresponding enhancement in activity in the frontal pole, namely area 10. I am wondering therefore whether such reciprocal changes in activity are reflections of the reciprocal functional interactions that exist between different areas of prefrontal cortex?

D. R. Weinberger (*Clinical Brain Disorders Branch, National Institute of Mental Health, Neuroscience Center at St. Elizabeths, 2700 Martin Luther King Jr Ave, SE, Washington, D.C., 20032, U.S.A.*). Dr Robbins's question necessitates first some further clarification of our results. What we found was an area within dorsolateral prefrontal cortex that was activated by the control subjects. This is the same area of DLPFC that we have previously seen activated in several different cohorts of normal subjects with this task. The patients in this study as a group did not significantly activate this area, but within the patient group, the more active the area was, the better the patient tended to perform. We also saw a prefrontal area that the patients significantly activated, but that the normal group did not. However, within the normal group those subjects who had more activity in this area tended to perform worse. This area was not a frontopolar region, but it was more anterior than that typically activated by healthy subjects. With regard to deactivation, the typical practice of comparing brain activity during a condition of interest to a 'baseline' condition has two possible consequences that have implications for so-called de-activation. The first can occur if a shift in global activity – or even a trend toward one – occurs in one condition but not the other, and if the shift is not uniform across the brain but rather is accounted for by large regional changes. In this scenario, when the regional data are 'normalized' to the global mean, as they usually are in order to minimize variance, a region of the brain that actually increased in the condition of interest, but increased less than other areas, will appear to be deactivated when normalized data are compared to the baseline condition. Absolute rCBF data, if collected, can help with this. The second possible consequence has to do with the details of what subjects are doing and experiencing during the 'baseline' condition and how active an area of interest is during that 'baseline'.

Either or both of these occurrences may be considered artefacts, but this decision must rest on *a priori* knowledge of the experimental design. Likewise, interpretation, in a neural systems sense, of brain activity being lower in one condition than another depends upon an understanding of the experimental conditions and of the functional anatomy that is recruited.

C. D. Frith (*Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London WC1N 3BG, U.K.*). I am confident that the deactivations sometimes seen in functional neuroimaging studies are not an artefact of data analysis, as the changes observed are very focal. However, deactivations are difficult to interpret as we have no measure of absolute activity, only activity relative to another condition. In a region where there is more activity associated with condition A than condition B, this could be due to activation in condition A or deactivation in condition B. How we interpret the differences depends in part on the paradigm and in part on theory. Many studies have shown that activation is affected by 'top down' attentional processes even when the actual sensory input remains constant. Thus, attention to colour, rather than motion in a visual display will cause relative activations of colour areas and relative deactivations of motion areas (Corbetta *et al.* 1991, *Science* **248**, 1556–1559). The activations and deactivations seen within prefrontal cortex could also be interpreted as reflecting attention to or competition between different cognitive processes. We have recently shown that activity in medial prefrontal areas is associated with an increase in 'stimulus independent thoughts' (McGuire *et al.* 1996, *Neuroreport*, in the press). These are thoughts that come to mind unbidden and unrelated to the task in which we are engaged. Behavioural studies (Teasdale *et al.* 1993, *Eur. J. Cog. Psychol.* 5, 417–433) have shown that SITS decrease in frequency when subjects are engaged in 'executive' tasks (of which the Tower of London is an example). Thus the 'deactivation' seen in medial prefrontal areas during the performance of many executive tasks could be reinterpreted as the activation of these areas in the control tasks associated with the greater occurrence of SITS. These reciprocal changes within prefrontal cortex could be the direct effect of functional interactions within this region or the result of influences from some other region such as the anterior cingulate cortex. The activation of frontal pole that Professor Weinberger has shown to be associated with impaired performance on the WCST could reflect task irrelevant cognitive processes (e.g. preoccupation with symptoms) or task

relevant, but inappropriate processes. These processes would compete with the appropriate ones instantiated in DLPFC. The nature of the inappropriate processes could be revealed by detailed behavioural studies.

L. WEISKRANTZ (*Department of Experimental Psychology, University of Oxford, South Parks Road, Oxford OX1 3UD, U.K.*). We have seen from neuroimaging studies that activity within the prefrontal cortex is disrupted in schizophrenia. It has also been shown that activity within a single brain area restricted to the prefrontal cortex appears to be related specifically to the 'theory of other peoples' minds'. However, lesions in the prefrontal cortex of humans do not produce schizophrenia and they do not result in the loss of a 'theory of other peoples' minds' that has been hypothesized to occur in autism. Therefore, what is the frontal contribution to these disorders and why is it evident from functional neuro-imaging studies but is not reflected in the deficits associated with frontal lesions?

D. R. WEINBERGER (*Clinical Brain Disorders Branch, National Institute of Mental Health, Neuroscience Center at St. Elizabeths, 2700 Martin Luther King Jr Ave, SE, Washington, D.C., 20032, U.S.A.*). Professor Weiskrantz offers an important caveat that applies to any activation mapping studies of patients with brain disorders. It is important that the interpretation of such data be informed by the results of lesion studies in both humans and experimental animals. We would tend to disagree, however, with his assumption that frontal lesions do not produce psychosis in humans. While lesions in adult prefrontal cortex, i.e. cortex that has developed and matured normally and is then damaged during adult life, are relatively rarely associated with psychosis, lesions of the developing prefrontal cortex may have a different effect. In fact, prefrontal lesions that occur or appear during adolescence are much more likely to manifest as psychosis than similar lesions occurring later in life (Weinberger 1987, *Arch. Gen. Psych.* **44**, 660–669). In a recent survey of psychopathology associated with the prefrontal lesion of metachromatic leukodystrophy, Hyde *et al.* (1992) pointed out that if the disease appears in early adulthood, it presents as a schizophrenia-like illness in the majority of cases (Hyde *et al.* 1992, *Arch. Neurol.* **49**, 401–406). The possibility that the basic cortical defect in schizophrenia is of developmental origin is consistent with an increasingly compelling database concerning the illness (Weinberger 1996, *Neuropsychopharmacology* **14**, 15–115).

C. D. FRITH (*Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, WC1N 3BG, U.K.*). There are, of course, other domains in which imaging studies and lesion data give discrepant results. Long-term memory tasks, for example, give rise to robust activity in prefrontal cortex, while almost nothing happens in medial temporal cortex. This is a dramatically different story from that told by the lesion data. That imaging studies and lesion data give different results is a good thing since otherwise one of the measures would be redundant. However, it is not yet entirely clear how to interpret these differences. In the case of schizophrenia, it is true that frontal lesions do not usually lead to hallucinations and delusions. On the other hand the negative features of schizophrenia are very similar to those associated with frontal lesions. One might speculate that hallucinations and delusions are due to aberrant activity in the frontal cortex rather than lesions. With regard to 'theory of mind' tasks, I think it is still early to say whether or not these are impaired by frontal lesions. Robin Morris at the Institute of Psychiatry tells me that 'frontal' patients do have difficulty with these tasks. It is also important to take account of the difference between developmental and acquired disorders. Autism is certainly associated with biological abnormalities that are present from birth and many currently believe that the same is true of schizophrenia. I believe that developmental disorders are characterized by abnormal connections between brain areas. Such disorders would not therefore resemble those associated with localized lesions.

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