

Neuropsychological dysfunction in depression: the relationship to regional cerebral blood flow

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SYNOPSIS The relationship between neuropsychological test performance and regional cerebral blood flow (rCBF) was examined in 29 patients meeting Research Diagnostic Criteria (RDC) for major depression. Following a comprehensive neuropsychological assessment two subsets of tests, comprising tests that discriminated between patients and controls or between patients with varying degrees of global cognitive impairment, were selected. These subtests were entered into a principal components analysis (PCA) which generated a two-factor solution, accounting for 50% of the overall variance in test scores. Individual patient loadings on each of these factors were subsequently correlated with regional cerebral blood flow (rCBF), as measured by positron emission tomography (PET). Both factors demonstrated significant correlations with rCBF in the medial prefrontal cortex and frontal polar cortex while for each factor there were also unique patterns of correlations with posterior brain regions. The findings provide additional evidence that neuropsychological deficits in depression are associated with abnormalities in regional brain function and in particular with the function of the medial prefrontal cortex.

INTRODUCTION

Intellectual deficits are an almost invariable component of clinical depression. Depression related cognitive deficits range in severity from mild, subclinical impairments, to pervasive global deficits, frequently referred to as depressive pseudodementia (Kiloh, 1961; Abrams & Taylor, 1987; Golinkoff & Sweeney, 1989; Watts *et al.* 1990). Neuropsychological studies have characterized depression related cognitive deficits as affecting mnemonic, attentional and psychomotor functions (Miller, 1975; Weingartner *et al.* 1981; Calev & Erwin, 1985; Golinkoff & Sweeney, 1989). Parallel findings to those obtained in depressed patient populations have been described in normal subjects following the experimental induction of depressed mood (Blaney, 1986; Ellis & Ashbrook, 1991).

The underlying nature of depression related cognitive deficits has been a source of extensive

theoretical debate. Psychological theories include motivational deficits, lack of effort, poor encoding strategies or defective processing resources (Weingartner *et al.* 1981; Cohen *et al.* 1982; Widlocher & Hardy-Bayle, 1989). How such putative psychological mechanisms relate to underlying brain systems remains a matter of conjecture.

The role of the medial prefrontal cortex in the cognitive impairment of depression has been suggested by findings of decreased rCBF in this brain region in a selected subgroup of primary depressed patients with severe global cognitive dysfunction (Dolan *et al.* 1992). Furthermore, a significant correlation has been demonstrated between a measure of global cognitive function and decreased rCBF in the medial prefrontal cortex in an extended series of patients selected solely on the basis of meeting criteria for primary depression (Bench *et al.* 1993*a*).

A neuropsychological study of the patients that comprise the present investigation has indicated deficits in neuropsychological functioning across a range of tests involving language, memory, attention and behaviour regu-

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lation, in patients with primary depression. The present investigation specifically addresses the nature of the relationship between neuropsychological test performance in depression and underlying brain function as measured by regional cerebral blood flow (rCBF). On the basis of our previous studies we predicted that neuropsychological test profiles in depression would be related to rCBF in the medial prefrontal cortex. While our previous studies, based on a measure of global cognitive impairment, have shown such an association it remained to be determined whether individual aspects of cognitive function would show a similar pattern of association or whether other brain regions might be involved in specific components of the cognitive impairment of depression. To limit the number of correlations between neuropsychological test scores and underlying rCBF we used a multivariate statistical technique, principal components analysis, in what is essentially an exploratory investigation.

METHOD

The details of subject selection and clinical assessments are described in the companion paper (Brown *et al.* 1994). To summarize, 29 (19 male; 10 female) depressed patients who satisfied Research Diagnostic Criteria for depression (RDC) were included in the study (Endicott & Spitzer, 1978). Patients were rated as having moderate to severe depression (mean = 25; s.d. = 4.2; range 17–34) on the 17-item Hamilton Rating Scale for depression (HAM-D). The mean age of the sample was 58 years (s.d. = 13). Half of the patients ($N = 14$) were taking antidepressant medication at the time of the assessments.

Neuropsychological tests

The details on neuropsychological testing of the patients are provided in the companion paper (Brown *et al.* 1994). The depressed patients were compared with a matched control group ($N = 16$) of non-depressed normal volunteer subjects. In this comparison neuropsychological impairments were evident across a range of tasks in the depressed subjects compared to the controls. Within the patient sample a separate profile of

neuropsychological impairment was evident that related to overall level of cognitive functioning. On this basis, the subsets of tests that discriminated depressed patients from normal control subjects, and those that discriminated within the patient group between those with varying degrees of global cognitive impairment were selected for further analysis. The specific subset of test selected are listed in Table 1.

Principal components analysis of neuropsychological data

In view of the intercorrelations of the patient scores on the selected neuropsychological tests, and to reduce the number of correlations with rCBF, scores on the individual tests were subjected to a principal components analysis (PCA) using an orthogonal rotation solution. PCA is a multivariate statistical technique used to examine the relationships among a set of correlated variables, in this case neuropsychological performance across different tests, which transforms the original set of variables to a new and smaller set of uncorrelated variables called principal components. The new variables are ranked in decreasing order of importance so that the first principal component accounts for as much as possible of the variation in the original data. The PCA, computed using the Statistical Package for Social Sciences for IBM compatible Personal Computers (SPSS/PC+) (Norušis, 1988), generated a two-factor solution with eigenvalues greater than 1 which accounted for 50% of the variance in test performance. Individual patient weightings on each of these two factors were subsequently correlated with rCBF.

PET methods

Regional cerebral blood flow was measured under resting conditions, in a quiet darkened room, with the subjects supine in the PET scanner (CTI model 931-08/12). Subjects were asked to close their eyes during the examination but no other instructions were given. ^{15}O xygen in the form of C^{15}O_2 mixed with air was administered via an oxygen mask according to an established protocol. A single scan was acquired over the final 10 min period of an 18 min inhalation and arterial blood samples were taken via an indwelling 22 g catheter at 0, 5 and 10 min into the acquisition period. A

Hanning filter with a cut-off frequency of 0.5 was used in the reconstruction of the images giving a transaxial resolution of 8.5 mm. All scans were performed on the same equipment using the same methods over a 3-year period.

Image analysis

Image analysis was performed using SPM software (MRC Cyclotron Unit, London, UK) on a SPARC 1 workstation (Sun Microsystems Inc, Surrey, UK) using an interactive image analysis software package (ANALYZE, Biodynamic Research Unit, Mayo Clinic, USA). Calculations and image matrix manipulations were performed in PRO MATLAB (Mathworks Inc, New York).

Stereotactic normalization

Each reconstructed rCBF scan consisting of 15 primary transverse planes was interpolated to 43 planes to render the voxels approximately cubic. The data were then transformed into a standard stereotactic space (Friston *et al.* 1990, 1991a). Such transformation of the data allows for voxel by voxel averaging of data across subjects. In the standard space 1 voxel represents $2 \times 2 \times 4$ mm in the x , y and z dimensions, respectively, allowing direct cross reference to the anatomical features of a standard stereotactic atlas (Talairach & Tournoux, 1988). A Gaussian filter 10 pixels wide was applied to smooth each image to accommodate inter-subject differences in gyral and functional anatomy and to suppress high frequency noise in the images.

Detection of significant correlations between neuropsychological function and rCBF

Differences in global activity between subjects were removed by analysis of covariance on a voxel by voxel basis with global counts as covariate according to an established methodology (Friston *et al.* 1990). For each voxel in stereotactic space the analysis of covariance generated an adjusted mean rCBF value (normalized to 50 ml/dl/min) and an associated adjusted error variance. The subsequent analysis was aimed at identifying the brain regions where rCBF correlated significantly with the profiles of neuropsychological functioning. This was achieved by correlating individual's scores on each of the two factors, derived from the PCA

analysis, with rCBF. The volume examined was limited to planes for which a complete data set was available for each subject. Pixels at which there were significant correlations with each of the factors were identified and the result set of r values were displayed as a correlation statistical parametric map (SPM $\{r\}$), within the stereotactic space, plane by plane and as projections onto renderings of the medial and lateral cortical surfaces of the brain (Friston *et al.* 1991b).

RESULTS

The findings from the principal components analysis of the neuropsychological data, using a varimax rotation, are summarized in Table 1. This analysis generated a 2-factor solution accounting for a total of 50% of the total test variance. The first factor, with high loadings from memory related items, accounted for 32% of the variance. The second factor, with high loadings from attentional items, accounted for 18% of the variance. Medication status bore no systematic relationship to patient loadings on either of these factors. The patient loadings on each of the PCA factors were subsequently correlated with rCBF. The omnibus significance of these correlations, positive and negative, was determined by comparing the observed *versus* the expected correlations using the χ^2 statistic. Only positive correlations were significant in these analyses.

Correlations with the first principal component (memory) and rCBF

Significant correlations with rCBF ($P < 0.05$) and patient loadings on the memory factor were evident over an extensive area of the anterior medial prefrontal cortex. These correlations are displayed as an SPM $\{r\}$ in Fig. 1A. The areas of significant correlations encompassed the medial prefrontal and frontal polar cortical regions and extended from -8 to $+36$ mm above the AC-PC line. The specific regions included the cingulate cortex (BA 32 and BA 24) extending from -8 to $+8$ mm and cingulate cortex (BA 32) from 16 to 24 mm above AC-PC line; the medial frontal gyrus (BA 10; BA 9) extending from -8 mm through to $+36$ mm; and the superior frontal gyrus (BA 10; BA 9) extending from $+4$ to $+36$ mm. Posteriorly, there were significant bilateral correlations with areas that

Table 1. Results of factor analysis of neuropsychological tests with factor loadings

	Factor 1	Factor 2
Eigenvalue	5.1	2.9
% Variance	32%	18%
Paired associated learning - total (E)	0.78	-0.07
Recognition memory - categorized word list	0.77	-0.11
Paired associated learning - 1 h delay (E)	0.70	0.05
Recognition memory - unrelated word list	0.64	-0.52
Recall of unrelated word list	0.57	0.17
Rey auditory-verbal learning - 1 h delay	0.57	0.33
Memory, immediate recall (logical memory)	0.58	0.56
Recognition bias - unrelated words	-0.34	0.77
Serial sevens	0.39	0.74
Brown Peterson (STM) - 30 s delay	0.21	0.67
Digit span backward	0.43	0.63
Schonnel (total)	0.38	0.61*
Weigl categorization test	0.00	0.55

* Schonnel reading test showed a significant improvement on recovery from depression indicating that poor performance at index assessment may be due to failure of patients to attend to precise spelling of more difficult words.

encompassed the retrosplenial cortex, the pre-cuneus and posterior cingulate cortex (BA 31, 30 and 23) extending from +16 to +24 mm. Bilateral correlations were also evident with the inferior parietal lobule extending to the angular gyrus from +20 to +28 mm above AC-PC line, and with the middle temporal gyrus (BA 21) extending from -8 to +4 mm. Finally, correlations were evident on the right with the superior temporal gyrus (BA 42/22) from +8 to +16 mm above AC-PC line.

Correlations with second principal component (attention) and rCBF

Significant correlations ($P < 0.01$) were evident for the attention factor with both anterior prefrontal and posterior brain regions. These correlations are displayed as an SPM{t} in Fig. 1B. Anteriorly, the correlations included the superior frontal gyrus (BA 10) extending from +16 to +24 mm and the medial frontal gyrus from +20 to +36 mm (BA 10/9) above the AC-PC line. Posteriorly, bilateral correlations, more extensive on the right, were seen with the inferior post central gyrus (BA 40, 42, 43) from +16 to +24 mm and inferior parietal lobule (BA 40) through +20 to +24 mm. Finally, significant correlations were seen with the posterior aspect of the middle temporal gyrus

confluent with the left angular gyrus (BA 39) extending from +16 through to +24 mm.

DISCUSSION

The central hypothesis of the present study, namely that neuropsychological impairment in depressed patients is related to rCBF in the medial prefrontal cortex, has been confirmed by the present findings. The main profile of neuropsychological dysfunction identified by the first principal component, accounting for 30% of the variance, showed significant correlations with rCBF that extended from the frontal pole, through the medial prefrontal cortex, including the anterior cingulate cortex, to the orbital frontal cortex. Likewise, the second principal component, accounting for 18% of the variance, showed significant correlations with rCBF that overlapped topographically with the prefrontal areas reported for factor 1, though excluding the anterior cingulate. These anterior correlations from the second factor were, however, more restricted in extent than for factor 1, being principally confined to the superior and medial frontal gyrus. This pattern of association between increasing neuropsychological impairment and decreased rCBF in the medial prefrontal and frontal polar cortex is identical to a finding reported on a subgroup of these same patients who were selected on the basis of a global measure of cognitive impairment (Dolan *et al.* 1992). The findings also mirror those reported on an extended sample of 40 patients where a global measure of cognitive function was highly correlated with decreased rCBF in the medial prefrontal cortex (Bench *et al.* 1993a). The present findings, using more refined and specific measures of cognitive function, indicate a more extensive pattern of prefrontal correlations than those previously reported. However, the present findings are preliminary in nature and require confirmation in separate hypothesis led investigations.

The first factor had loadings derived principally from items related to memory and learning. The finding of significant correlations between this factor and an extensive region of the medial prefrontal cortex might be considered surprising as this cortical region is not generally associated with memory function (Amaral, 1987). The finding suggests that the association

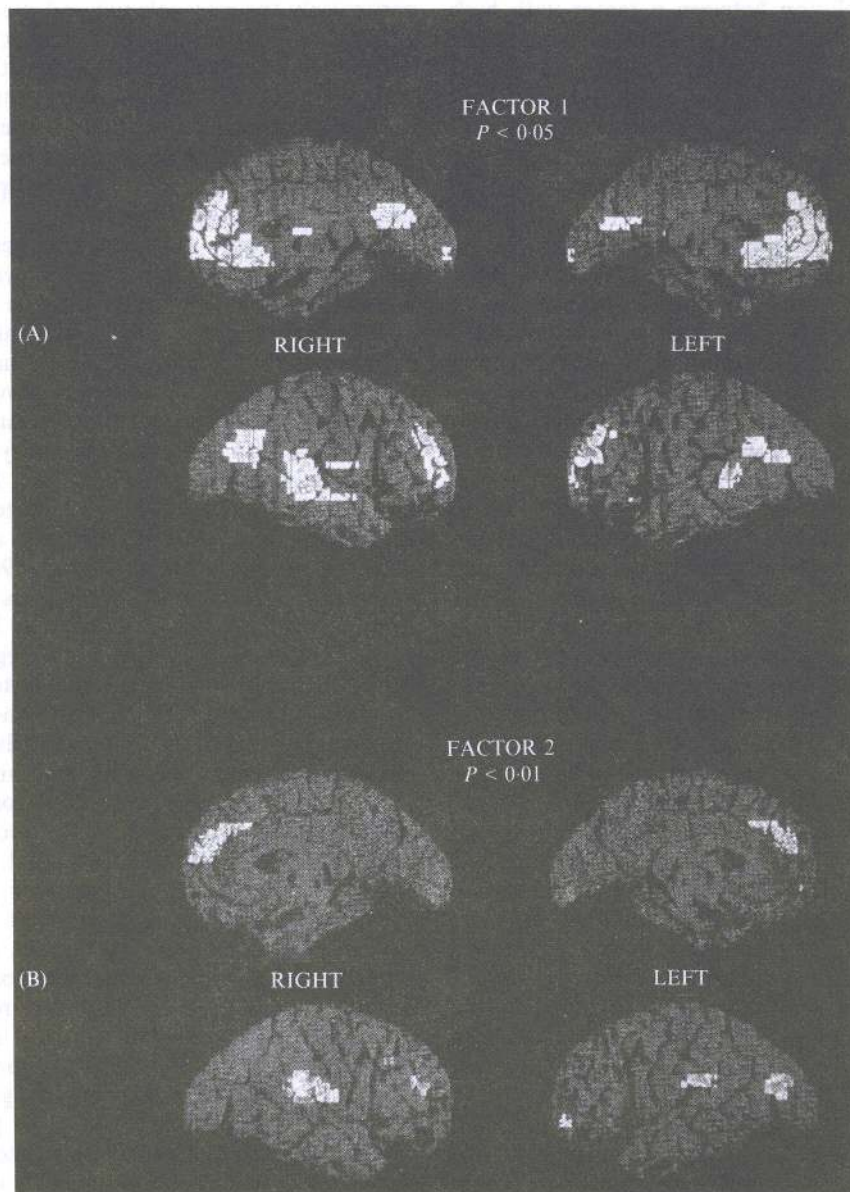


FIG. 1. Correlation SPMs, displaying pixels rendered on the medial and lateral surfaces of both cerebral hemispheres, at which there are significant positive correlations between rCBF and patient loadings on each of the neuropsychological factors ($P < 0.05$ for factor 1; $P < 0.01$ for factor 2).

of decreased prefrontal brain function with impaired mnemonic function in depression is not attributable to a dysfunction within a core memory system. A corollary of this finding, therefore, is that impaired mnemonic function in depression has different neuropsychological characteristics from those found in association

with a deficit in a primary memory system as in temporal lobe or diencephalic amnesia. Indeed, a striking feature of the pattern of memory impairment displayed by the patients was the selective nature of the task deficits. In particular, patients showed maximal impairment in more effortful or demanding memory tasks.

The correlation between a factor with high loadings from memory related items and rCBF in the medial prefrontal cortex is suggestive of a role for this cortical region in aspects of memory. An increasing body of evidence indicates that certain aspects of memory function require the integrity of the frontal lobes. For example, frontal lesions are associated with deficits in temporal ordering of both recent and remote memories (Milner *et al.* 1985; Moscovitch, 1989; Shimamura *et al.* 1990). Patients with prefrontal lesions have deficits in free recall of unrelated words at 24 h (Shimamura *et al.* 1991). Frontal lobe excisions result in impairments on memory tasks requiring free recall but little impairment when encoding and retrieval strategies are supplied (Jetter *et al.* 1986). Patients with frontal excisions also show inordinate susceptibility to the effects of interference (Rocchetta & Milner, 1993). Depression-related memory deficits may thus be attributable, at least in part, to involvement of a prefrontal system involved in attentional or effortful processes of memory rather than involvement of core memory processes *per se*. This is consistent with the view that mnemonic deficits in depression primarily involve tasks that require sustained effort (Cohen *et al.* 1982). The neuropsychological characterization of the present patients indicated that mnemonic impairment was most clearly related to the presence of depression with mnemonic deficits in particular discriminating between patients and control subjects. In this context it is noteworthy that increasing memory impairment is associated with decreased function in the anterior cingulate cortex, an area that has been shown to be dysfunctional in primary depression (Bench *et al.* 1992).

Although the memory factor was associated with rCBF in prefrontal regions there were also significant correlations with posterior brain regions that encompassed the retrosplenial, precuneus and posterior cingulate cortices. Correlations were also evident with an area that included the middle temporal gyrus extending to the superior temporal gyrus, particularly on the right. Lesions of the retrosplenial area have been associated with selective memory impairment (Rudge & Warrington, 1993). All of the identified areas have been implicated in the functional anatomy of auditory-verbal long-term memory (Grasby *et al.* 1993). Anatomically these regions,

particularly the retrosplenial and posterior cingulate areas, have important connections with the medial temporal cortex and with anterior thalamic nuclei both of which are implicated in memory function (Rosene & Van Hoesen, 1977). Furthermore, a dense amnesia has been reported following focal damage to the retrosplenial and surrounding cortex (Valenstein *et al.* 1987). Correlations were also evident between the memory factor and the angular gyrus region bilaterally. This association may be explicable by the fact that the memory items were all auditory-verbal in nature. An area that includes the angular gyrus has been shown to be important in lexico-semantic processing which is a requirement in the type of memory task used in the study (Demonet *et al.* 1992). Lesions of the posterior temporal-parietal cortex, on the left or bilaterally, are associated with associative semantic memory deficits (Luria, 1966). Thus, the memory deficit that distinguishes depressed from non-depressed individuals may be a product of dysfunction in two brain regions; one frontal based and relating possibly to strategic or effortful aspects of memory and another posterior region linked to areas involved in core memory and lexico-semantic functions.

The second factor, with high loadings on attentional related items, was also strongly correlated with rCBF in the medial prefrontal cortex as well as with the superior prefrontal cortex. This finding is consistent with the viewpoint that the prefrontal cortex has a pre-eminent role in the maintenance of goal directed behaviours particularly those that require the suppression of external or internal interfering influences (Fuster, 1989). The prefrontal cortex has been implicated in tasks requiring voluntary attention (Wilkins *et al.* 1987). In particular, medial prefrontal lesions impair functions that require sustained attention to action or thought processes (Fuster, 1989). Lesions in the anterior medial prefrontal cortex have been associated with central gaze fixation deficits (Paus *et al.* 1991). A number of PET studies, in normal subjects, have highlighted the role of the medial prefrontal cortex in attentional processes. In studies of selective attention, using the Stroop paradigm, activations of the cingulate and frontal polar cortex have been reported (Pardo *et al.* 1990; Bench *et al.* 1993*b*). Significant activations in the anterior medial prefrontal

cortex have also been reported in a study of working memory where the specific task involved the external monitoring of auditory verbal material (Petrides *et al.* 1993). The presence of significant correlations between the anterior medial prefrontal cortex and a neuropsychological factor with high loadings from attentional tasks suggests that a component of the cognitive impairment of depression is associated with an involvement of a brain system subserving selective attention. In view of the fact that attentional items distinguish best between patients with varying degrees of global cognitive impairment it can be hypothesized that, within a population of depressed patients, increasing cognitive impairment is attributable to greater involvement of medial and superior prefrontal cortices.

Significant correlations were also seen between the second principal component and posterior brain regions. The areas included a region extending from inferior post central gyrus to the inferior parietal lobule. A similar area has been shown to be activated during the performance of short-memory tasks (Grasby *et al.* 1993; Paulesu *et al.* 1993). The observed association may be due to the fact that one of the contributory items to the second principal component was a short-term memory item (the Brown-Peterson task). The separate correlations with a posterior area that included the angular gyrus region is suggestive of a role for this region in attentional processes. Although the functions of this cortical region are multimodal they include a system subserving attention and orientation, particularly to stimuli of motivational significance (Heilman *et al.* 1970; Mountcastle & Lynch, 1975; Lynch, 1980; Pandya *et al.* 1981; Mesulam, 1983). We have previously demonstrated decreased function in this region in a comparison of patients with depression and normal controls (Bench *et al.* 1993a).

The most significant associations for both principal components, in terms of spatial extent, were with rCBF in the medial prefrontal cortex. There are two possible explanations for this finding. First, a common pathophysiology affecting this brain region may contribute to both factors due to the possibility that different functions are represented in the medial prefrontal cortex. An alternative possibility is that the psychological factors, despite the orthogonal loadings, share a common psychological com-

ponent mediated by the prefrontal cortex. An obvious dimension shared by both factors would appear to be a component related to sustained attention. In a *post hoc* analysis of the data, using an unrotated factor solution, three of the items loading on factor 2 (serial sevens, digit span backwards and the Schonell) now demonstrated highest loadings on a main factor which included the memory items in factor 1 of the rotated factor solution. Furthermore, this factor was even more highly correlated with rCBF in the medial prefrontal cortex than either of the factors from the rotated factor solution. This, therefore, supports the possibility that the correlations with rCBF in the medial prefrontal cortex for both rotated factors might be attributable to a common component such as attention. However, the second factor from the unrotated solution also showed a pattern of correlation with rCBF in the medial prefrontal cortex.

Shallice, from a cognitive neuropsychological perspective, has proposed a theory of prefrontal function whose role is the modulation of lower-level systems through the activation or inhibition of particular schemata (Norman & Shallice, 1986). A similar concept of a central processing module is implicit in other neuropsychological theories such as the central monitor of Weiskrantz (1988) and the central executive of Baddeley (1992). This system, the supervisory attentional system (SAS), is required in the performance of non-routine actions, and is assumed to be located anteriorly in prefrontal cortex. A consequence of failure within this putative system is a deficit in the attentional control of behaviour. In other words the SAS fails to maintain task related activity in the face of other distracting sources of information (Shallice *et al.* 1989). The strong associations between prefrontal rCBF and cognitive function during episodes of clinical depression is suggestive of a neurophysiological basis to the observed neuropsychological deficits. The medial prefrontal deficits in depressed patients with cognitive impairments could, therefore, be interpreted as a dysfunction in one or more components of a central executive system involved in the regulation of action, as required in strategic memory function, or the inhibition of prepotent response tendencies, as required in attention demanding tasks.

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