

Subcortical hypoperfusion following surgery for aneurysmal subarachnoid haemorrhage: Implications for cognitive performance?¹

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The incidence and severity of cognitive deficits after surgery for aneurysmal subarachnoid haemorrhage and their relationship to aneurysm site remains controversial. The aim of this study was to investigate the pattern of regional cerebral blood flow which exists in patients one year post-surgery and to identify whether different patterns exist which may be related to the type of cognitive deficit or the location of the aneurysm. 62 patients underwent cognitive assessment and HMPAO SPECT imaging at a mean time of 12 months following surgery. Results were compared to those from healthy control subjects ($n = 55$ for neuropsychological testing; $n = 14$ for SPECT imaging). In the patient group, significant stable cognitive deficits occurred in all cognitive domains but no cognitive measure differentiated aneurysm site. On SPECT images, statistical parametric mapping identified a large common area of subcortical hypoperfusion in the patient group as a whole. The findings of this study suggest a possible link between reduced subcortical function and the extent and severity of cognitive deficits.

Keywords: Radionuclide, blood flow, haemorrhage, cognition, tomography

1. Introduction

Subarachnoid haemorrhage is defined as an escape of blood from an intracranial blood vessel into the subarachnoid space, the commonest cause of which is the rupture of a cerebral aneurysm. It accounts for 5% of all strokes and for 45% of those occurring between the ages of 35 and 45, with an estimate of annual incidence of between 6 and 20 per 100,000 of the population per annum [31]. Outcome from aneurysmal subarachnoid haemorrhage is not optimal, and it has been reported that good neurological recovery is achieved in only around one half of the patients [7,17]. Even when the neurological outcome is good, there is evidence of long term clinically significant cognitive impairment in a large proportion of patients [14]. For example, the studies of Sveland et al. [25] and Stegen and Freckmann [28] showed that one year after major aneurysmal subarachnoid haemorrhage, few if any patients displayed a full recovery with no signs of psychosocial or cognitive disturbance, although a third of such patients showed sufficient recovery to enable them to return to some kind of work.

The causes of such cognitive impairment remain controversial, and the direct effects of aneurysm rupture, surgical factors and the location of the aneurysm have all been implicated [4,16,27,31]. These issues are unlikely to be resolved until a clearer understanding is achieved of the clinical factors associated with cerebral aneurysms that underlie cognitive deficits and until the cognitive outcome is consistently compared to measures of structural brain damage and regional cerebral blood flow. The long term effects of subarachnoid haemorrhage on regional cerebral blood flow have not been studied in detail by functional neuroimaging techniques. Single photon emission tomography (SPECT) using the ligand ^{99m}Tc HMPAO (hexamethyl propylene amine oxime) offers the opportunity to study alterations in regional cerebral blood flow in this group of

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patients by non-invasive methods. There are a limited number of reports in the literature on the use of HMPAO in the early post-operative period following surgery for subarachnoid haemorrhage [30] and very few reports on the late effects [3,26]. The aim of the present study is to investigate the patterns of regional cerebral blood flow which exist in patients one year following surgery for subarachnoid haemorrhage and to identify whether different patterns exist which may be related to the type of cognitive deficit or the location of the aneurysm.

2. Materials and methods

The data presented in this paper form part of a larger prospective, longitudinal study designed to investigate the relationship between subarachnoid haemorrhage, its treatment, and cognitive and neuropathological outcome.

2.1. Patients

The study group comprised all patients presenting to the Sheffield Department of Neurosurgery during the period from January 1995 to December 1996, with a diagnosis of a first subarachnoid haemorrhage from a ruptured cerebral aneurysm and who were treated by neurosurgery. Subarachnoid haemorrhage in these patients was confirmed by Computed Tomography (CT) examination or lumbar puncture and the presence of aneurysm was confirmed by angiography. Patients were excluded from the study if they were aged over 70 at the time of recruitment, if they had had a previous brain insult or previous neurosurgical intervention or if they had any other condition known to impair cognitive function.

109 patients were recruited into the study. 8 patients died post-operatively and one remained vegetative throughout the period of study. Of those remaining, 88 patients underwent both SPECT scanning and neuropsychological investigation 12 months after surgery. There were 35 males and 53 females. The mean age of the group was 48 years (range 20 to 70 years). The distribution of aneurysm site in this group is given in Table 1. Detailed data analysis was carried out on a subset of 62 patients from the study group. The demographics of this subgroup are given in Table 2. There were no differences between the patient groups, subdivided according to aneurysm site, with respect to the severity of subarachnoid haemorrhage, as reflected by the clinical state on admission (World Federation of Neurosurgeon score [9]) and the distribution of blood on initial CT

Table 1
Distribution of aneurysm site – all patients

Site of aneurysm	n
Anterior communicating artery (ACoA)	41
Left internal carotid artery (L ICA)	4
Right internal carotid artery (R ICA)	2
Left middle cerebral artery (L MCA)	5
Right middle cerebral artery (R MCA)	12
Left posterior communicating artery (L PCoA)	9
Right posterior communicating artery (R PCoA)	10
Pericallosal artery	2
Basilar	1
L posterior inferior cerebellar	1
L superior cerebellar	1

examination (Fisher score [10]). Similarly, there was no difference between the groups with respect to neurological outcome at 12 months following surgery, as assessed by the Glasgow Outcome Scale (GOS) [15].

2.2. Control subjects

For SPECT brain imaging a group of 14 control subjects was recruited. There were 9 males and 5 females, with a mean age of 53 years (range 45 to 60 years). All control subjects were screened for evidence of personal or family history of neurological or psychiatric problems, prior to inclusion. For neuropsychological testing, an age matched group of 55 control subjects was available for study. There was no significant difference between the current verbal IQ (WAIS-R) of these subjects and the premorbid IQ of the patient group.

3. Investigations

All subjects underwent neuropsychological testing and brain SPECT imaging at a mean time following surgery of 365 days (range 344 to 394 days). In addition, as part of the larger study, all patients underwent magnetic resonance (MR) imaging at 12 months following surgery (MR compatible clips were used at surgery).

3.1. SPECT imaging

Each subject was given an intravenous injection of 500 MBq of ^{99m}Tc HMPAO under quiet resting conditions (eyes closed, ears plugged). Imaging was carried out one hour post-injection using an Elscint Helix dual headed gamma camera equipped with low energy parallel hole collimators. Data acquisition was performed using a full 360 degree rotation of each detector, with

Table 2
Demographics and clinical indicators of patients ($n = 62$) and control subjects

Group	n	Age	M : F	Fisher	WFNS	G.O.S	premorbid IQ
AcoA	30	49.9	14:16	3.2	1.4	1.3	104.8
Other aneurysms	32	47.4	9:23	2.8	1.4	1.1	105.9
SPECT controls	14	53.4	9:5	n/a	n/a	n/a	n/a
Neuropsychological controls	55	48.2	19:36	n/a	n/a	n/a	106.8

an image matrix size of 64^2 , a zoom factor of 2 and 120 projections per detector. The acquisition time per projection was calculated at the beginning of each scan to give a total of 6 million counts for the two detectors combined, which is equivalent to 25000 counts per projection per detector. Mean acquisition time per projection was 17 seconds (range 12 to 32 seconds).

3.2. Neuropsychological testing

Each assessment followed the same protocol. Patients were contacted by telephone approximately a week before the assessment was due and an appointment convenient to them was made to attend the Department of Clinical Neurology at the Royal Hallamshire Hospital for a day. All assessments were made within three weeks of the due date.

Assessments were completed, when possible, in a single session. Where pain, fatigue or confusion made this impractical, testing was completed within a period of one week. The neuropsychological test battery included tests assessing intelligence, memory, executive function and attention, language, visual perception and affect, as detailed below. Each assessment took, on average, four hours to complete, although this varied between patients. Appropriate breaks within this session were given to minimise the effects of fatigue.

Intelligence

Pre-morbid intelligence was assessed using the National Adult Reading Test – revised [20]. Current intellectual functioning was assessed at each assessment using the following subtests of the WAIS-R [33]: digit span, vocabulary, similarities, arithmetic, picture arrangement and block design. These subtests were analysed separately rather than combining to form prorated IQ's, as an insufficient number of subtests were conducted to allow this.

Memory

Traditional paradigms were used to assess recognition and recall memory. Verbal recall was assessed using immediate and delayed (30 minutes) story recall. The story was made up of 20 memory units scored us-

ing the method proposed by Power et al. [22] giving 1 mark for an exact verbatim repeated unit and half a mark if either part of the unit was missing, or if the meaning of the unit was correctly expressed, but using different words. Nonverbal recall was assessed using a 30 minute delayed recall of a complex geometric design which was initially copied by the patient. Scoring used the criteria for the Rey-Osterreith figures [24] producing 2 scores: one which represented constructional skills and one for combined constructional skills and memory. As constructional deficits could be anticipated a 'rate of forgetting' score was calculated using the following equation:

$$\text{rate of forgetting} = \frac{(\text{copy score} - \text{recall score})}{\text{copy score}}$$

Verbal and non-verbal recognition memory were tested using a newly developed version of the Warrington recognition memory test (WRMT [32]). Immediate verbal memory span was assessed in the digit span subtest of the WAIS-R, and immediate spatial span was assessed using a computerized version of the Corsi block task [19].

Executive function and attention

Verbal and spatial working memory were assessed using a digit ordering task [6] and a subtest of the CANTAB battery. In the digit ordering test subjects were read a random selection of 7 digits (e.g. 5-3-6-2-7-2-1) were required to reorder the items in memory and repeat them in ascending fashion (e.g. 1-2-2-3-5-6-7). Each subject was given 15 trials. For each trial, 1 point was awarded for each digit placed in its correct position until a response broke the ascending sequence (e.g. 6 followed by 4). Maximum score was 7 per trial (total 105); if a subject reported more than 7 digits, only the first 7 were scored. Responses that did not come from the test presentation but, nevertheless, maintained ascending order were tolerated not scored. The spatial working memory task, (detailed in [19]), involves a systematic search of an array of boxes. Successful performance of this task requires memory both within a search and between searches of each trial. The task increases in difficulty with series of 3, 4, 6 and 8 box

problems. Two types of error are recorded (i) returning to a box that has already been looked in on the same search (within search error); (ii) returning to a box where a counter has been found on a previous search (between search error).

The ID/ED task from the CANTAB neuropsychological battery was administered to assess both problem-solving and set-shifting. The number of stages reached and the number of trials required to successfully achieve the extra-dimensional shift were recorded, as these are the two measures that have been shown to be sensitive to frontal lobe dysfunction. The materials used and procedure followed was the same as that outlined in Downes et al. [8].

A second task used to assess cognitive set-shifting was the alternating version of semantic fluency. Here, subjects were given 2 categories and asked to alternate between them, producing as many items as possible in 60 seconds, with the number of correct alternations recorded. In addition, standard category and letter fluency tasks were administered, both considered to require integrity of the frontal lobes.

The Trail Making Test [23] gives measures of divided attention and mental tracking. Part A simply requires the patient to draw a line, in sequence, of randomly displayed numbered circles. Part B is more complex requiring the patient to similarly draw a line between circles in the correct sequence, but this time to alternate between numbers and letters. By subtracting, or dividing, the time taken to complete Part A from time to complete Part B the psychomotor elements of the task are giving taken out, given a measure of divided attention and set shifting. These 2 measures are reported.

The CANTAB Tower of London is a computerized task based on an easier version of the Tower of Hanoi and is a test of planning ability. Patients are required to 'move' balls in 3 'stockings' so that they precisely match a given array, using 2 simple rules [19]. Owen et al. [21] reported that although frontal lobe patients are equally as capable of performing this task as matched controls, they are less efficient as evidenced by fewer problems solved in the minimum number of moves. In this study subjects were not told the minimum number of moves per solution; instead they were told to solve each problem in as few moves as they thought possible and were encouraged to plan the solution before beginning.

Language

Although many of the tasks in the test battery require language function, the majority have been placed with

tests of other cognitive domains. For example, although both letter fluency and semantic fluency are highly dependent on language function they have been included in the 'executive and attentional' domain as they are tasks that are traditionally considered to be 'frontal'. Similarly, the vocabulary and similarities subtests of the WAIS-R are language dependent, but will be considered in the section on intellectual ability, as this is the area that they usually represent.

The shortened Boston test of confrontational naming [13], whilst involving frontal lobe functions of retrieval, is a purer test of expressive language impairment. The test yields 3 scores which represent the number of items that were correctly named (a) without any cue (NC), (b) with a semantic cue (SC) and (c) with a phonemic cue (PC). 1 point is given to each of these 3 scores if the item is correctly named with no cue. If a semantic cue is required then 1 point is awarded to the SC and PC scores. If a phonemic cue is required then 1 point is awarded to the PC score alone.

Visuo-spatial function

Form discrimination is a test which requires the mental rotation of pairs of geometric shapes in order to make a decision as to whether they are the same. Both speed and accuracy are recorded, with a maximum accuracy score of 18. Speed is recorded as the sum of the response times for each item. In addition, the copy score of the complex figure indicates visuo-spatial constructional skill.

Affect

Affective disturbance was assessed using 2 questionnaires: The Beck Depression Inventory resulting in a single score [2] and the Profile of Mood State [18]. This decomposes into 6 subscores which reflect the level of disturbance in anger, anxiety, confusion, depression, fatigue and vigour. In addition, a total score, which subtracts the vigour score from the sum of all other scores, gives an index of total mood disturbance.

4. Data analysis

4.1. SPECT image analysis

The image data were reconstructed using filtered back projection with a Butterworth filter (order 3, cut-off $0.53 \text{ cycles cm}^{-1}$). Attenuation correction was performed using Chang's method [5] with a value for the attenuation coefficient of 0.123 cm^{-1} . At this stage

all data were registered using an affine transform to a local standard for brain images, to allow conformity for image display and presentation purposes.

The data were then analysed with statistical parametric mapping (using software from the Wellcome Department of Cognitive Neurology, London, UK), implemented in Matlab (Mathworks Inc, Sherborn, MA, USA). Statistical parametric maps are spatially extended statistical processes that are used to characterise regionally specific effects in imaging data. Statistical parametric mapping combines the general linear model (to create the statistical map or SPM) and the theory of Gaussian fields to make statistical inferences about regional effects [11,12,34]. Initially, all images were spatially transformed into the Talairach coordinate system [29] by registering to a template (an oxygen 15 labelled water positron emission tomography (PET) image) which already conformed to the standard Talairach space and which was supplied with the SPM software package. A twelve parameter affine (linear) transformation was used for this process. As a further pre-processing step the images were smoothed using an isotropic Gaussian kernel with full width half maximum (FWHM) of 12 mm.

The data were then corrected for differences in global blood flow between subjects using proportional scaling. This is a normalisation technique which takes differences in global blood flow into account by dividing each voxel by an image-derived estimate of global flow. The parameter which is most commonly used for this estimate is the mean count over the whole brain. However, for images which have large deficits in regional flow, the use of the whole brain mean for normalisation can lead to an underestimate of these deficits and artefactual increases in regional flow in other areas of the brain. In such circumstances, normalisation using counts only from a specific brain region which is uninvolved with the disease process is preferable from a theoretical standpoint. In this study, the only possible specific normalisation area was the cerebellum (all other brain areas having a likelihood of abnormal flow as a result of the disease process). In order to investigate the effects of using different normalisation regions, proportional scaling was carried out on two occasions to produce two distinct data sets: one set normalised to whole brain counts and the other normalised to counts in a three dimensional region of interest over the cerebellum.

For each normalised data set, statistical analysis was carried out to compare patient groups with control subjects. Three separate analyses were carried out:

- (i) All patients vs control subjects
- (ii) Patients who had anterior communicating artery (ACoA) aneurysms vs control subjects
- (iii) Patients who had aneurysms at locations other than the ACoA vs control subjects

The output from each statistical analysis is a three dimensional image or statistical parametric map in which the value at each voxel is related to the significance of any observed difference in perfusion at that location between the groups being compared. The output is initially a map of t-statistics for each and every voxel. This is then transformed to a unit normal distribution using a voxel by voxel t-to-Z transformation to produce a statistical parametric map ($SPM\{Z\}$) which obeys Gaussian statistics. The $SPM\{Z\}$ is thresholded at a chosen level (e.g. $Z = 3.09$, $p = 0.001$) and the resulting foci of significant voxels can then be characterised in terms of spatial extent and peak height. The significance of each region is estimated using distributional approximations from the theory of Gaussian Fields. The characterisation is in terms of the probability that a region of the observed number of voxels (or greater) could have occurred by chance, or that the peak height observed (or higher) could have occurred by chance over the entire volume analysed. This probability is termed a corrected p-value. In contrast to a Bonferroni correction, this corrected p-value provides a correction for the multiple non-independent comparisons which are implicit in the analysis.

4.2. Neuropsychological testing

For each of the tests, the data from the patient group as a whole were compared with that from the control subjects. Independent t-tests were used to identify group differences. As multiple comparisons were made a Bonferroni correction was used to minimise the possibility of Type 1 errors. Although some measures gave a skewed distribution, parametric statistics were used as the number of patients in each group was sufficiently large, and because the distribution was similar in both groups. Under such conditions, normal distribution violations can be withstood by the statistic.

To test the hypothesis that ACoA aneurysm patients represent a distinct population, 1 factor Analysis of Variance tested for differences between the ACoA group, controls and a group which combined all other aneurysm sites. Analysis was performed in this way as posterior communicating, internal carotid and middle cerebral aneurysm groups were too small to produce reliable statistics. Where simple effects were found,

post hoc analysis identified those groups which differed from each other. Bonferroni corrections were used, as before, to account for the use of multiple comparisons. With 37 measures analysed, Bonferroni correction adjusted p values as follows: $5\% = p < 0.001$; $1\% = p < 0.0002$; $0.1\% = p < 0.00004$. This is a very stringent correction, accounting for all comparisons since it can be argued that all cognitive functions are inter-related.

5. Results

5.1. SPECT imaging

A visual assessment of the SPECT brain images of the 88 subjects revealed 18 subjects who showed abnormal cerebellar uptake. Since the cerebellum was being used as a normalisation region in the statistical analysis, these subjects were excluded from further analysis. An additional five subjects, although meeting the initial inclusion criteria for the study, had undergone additional surgery during the twelve month period. These subjects were also excluded from further analysis. A further 3 patients with posterior circulation aneurysms were excluded from this analysis also as they represented too small a group to analyse individually, and are too anatomically distinct to meaningfully combine with other aneurysm sites. This left a total of 62 patients and 14 controls.

The results of the statistical analysis of the SPECT data on these subjects are shown in Figs 1 to 6. Figs 1, 2 and 3 represent the orthogonal maximum intensity projections of the thresholded statistical parametric map. The map is thresholded at an individual voxel value of $3.09 (p = 0.001)$ and clusters of voxels having a probability of chance occurrence of < 0.001 , when corrected for multiple comparisons, are displayed. The clusters demonstrated in the map thus represent collections of voxels where the $SPM\{Z\}$ value of each voxel is individually significant at an uncorrected p -value < 0.001 and the cluster has a significant spatial extent at a corrected p -value < 0.001 . Figs 4, 5 and 6 show selected orthogonal slices through the corresponding statistical parametric map (shown in colour), superimposed on a standard T1 weighted MR image, which is displayed in Talairach space, in order to provide some anatomical definition.

Figures 1 and 4 show the results of the statistical comparison of the patient group as a whole compared with control subjects. Figures 1(a) and 4(a) illustrate

the results obtained following whole brain normalisation of the data, while Figs 1(b) and 4(b) illustrate the corresponding results following cerebellar normalisation. A large, highly significant cluster of voxels is identified on both the whole brain and cerebellar normalised data. This represents a large central area of hypoperfusion involving the subcortical structures in the patient group compared with the control subjects. The pattern is similar with both types of normalisation but is less extensive on the whole brain normalised data. Interestingly, although on an individual patient basis cortical perfusion defects were frequently apparent, when the patient group is taken as a whole, there are no common areas of hypoperfusion in the cerebral cortex at this level of significance.

Figures 2 and 5 show the corresponding data for the patients with aneurysms of the anterior communicating artery compared with control subjects (Figs (a) and (b) illustrate the whole brain and cerebellar normalisation results respectively). A large highly significant ($p < 0.001$, corrected) area of central hypoperfusion is again apparent, this time extending anteriorly into the cortical area, consistent with the expected cortical site of damage from aneurysm at this location. Figs 3 and 6 show the results obtained from a statistical comparison of the remaining patient group (i.e. excluding those with aneurysms of the anterior communicating artery) with the control subjects (Figs (a) and (b) illustrate the whole brain and cerebellar normalisation results respectively). The significant area of subcortical hypoperfusion ($p = 0.007$, corrected) is clearly demonstrated on the whole brain normalised data (Figs 3(a) and 6(a)). With a height threshold of 3.09, this central cluster just fails to reach significance when corrected for multiple comparisons ($p = 0.12$) on the cerebellar normalised data (Fig 3(b) and 6(b)). However, this area is significant with cerebellar normalisation at a height threshold of 2.33 ($p < 0.05$, corrected). Interestingly, there are no common areas of significant perfusion deficit in the cortex in this heterogeneous group of patients when compared to controls.

5.2. Neuropsychological testing

Independent sample t -test analysis showed significant deficits in the patient group when compared to the matched control group in all cognitive domains except immediate memory and language, even once corrected for multiple comparisons. Lack of significant deficit in immediate memory (a measure of attentional capacity)

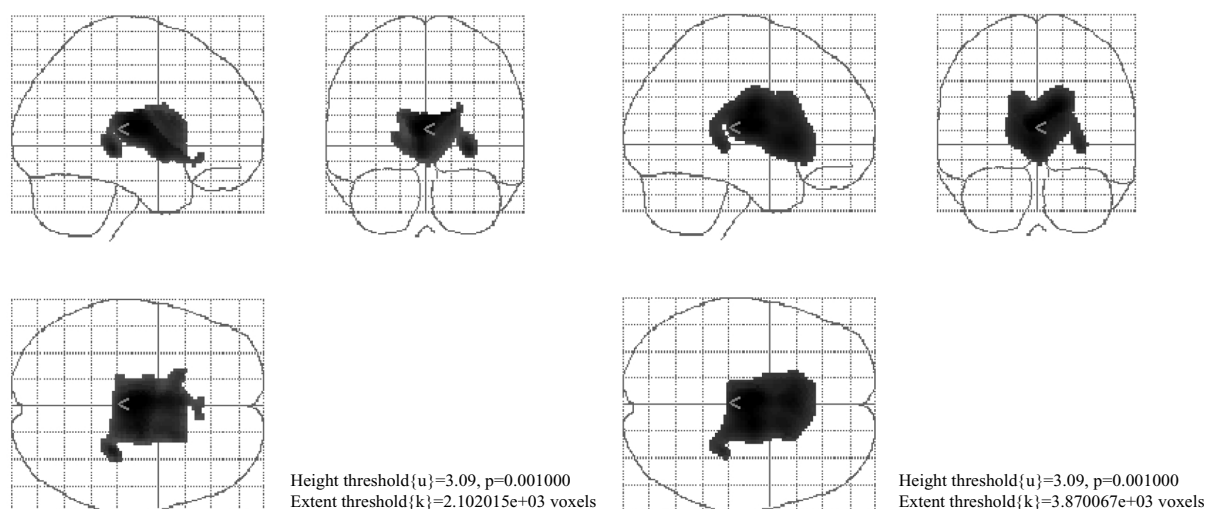


Fig. 1. SPM results comparing the patient group with control subjects; Fig. 1(a)(left): whole brain normalisation, Fig. 1(b)(right): cerebellar normalisation. The figures illustrate the orthogonal maximum intensity projections of the thresholded statistical parametric map. The map is thresholded at an individual voxel value of 3.09 ($p = 0.001$) and clusters of voxels having a probability of chance occurrence of < 0.001 , when corrected for multiple comparisons, are displayed.

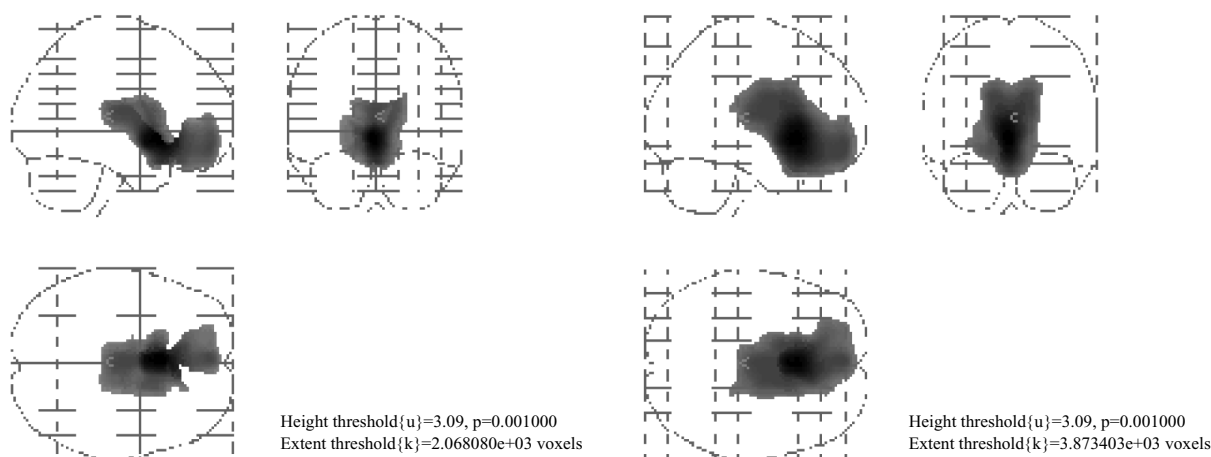


Fig. 2. SPM results comparing ACoA patients with control subjects; Fig. 2(a)(left): whole brain normalisation, Fig. 2(b)(right): cerebellar normalisation. The figures illustrate the orthogonal maximum intensity projections of the thresholded statistical parametric map. The map is thresholded at an individual voxel value of 3.09 ($p = 0.001$) and clusters of voxels having a probability of chance occurrence of < 0.001 , when corrected for multiple comparisons, are displayed.

and language implies that poor performance on other tests is not due to some pervasive perceptual problem.

Table 3 gives details of significant differences on individual tests. To summarise, the patient group were significantly impaired on all tasks except the arithmetic and similarities subtests of the WAIS-R, the Tower of London and the ID/ED set-shift, the error score on the spatial working memory task and the accuracy score for form discrimination.

When splitting the patient group into those with ACoA aneurysms and those with aneurysms at other sites a similar pattern is seen, although slightly weakened by the decreased degrees of freedom. However, the majority of significant differences continue to survive the correction for multiple comparisons. Tukey's h.s.d. *post hoc* analyses demonstrated no significant differences between the patient groups, as evidenced by no significant ACoA/'other' values. However, of note was the slightly higher degree of affective distur-

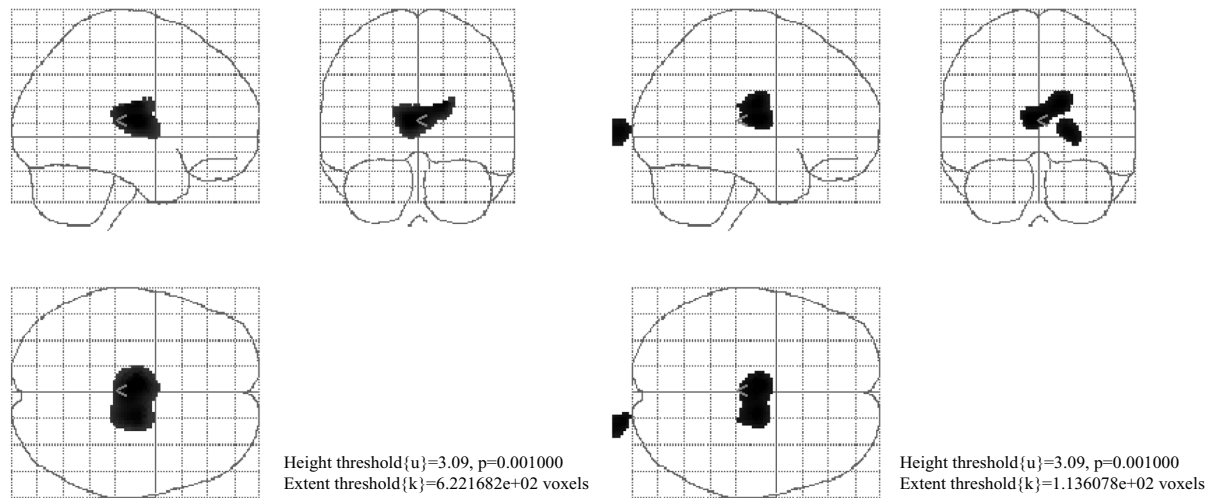


Fig. 3. SPM results comparing patients with aneurysms at sites other than ACoA with control subjects; Fig. 3(a)(left): whole brain normalisation, Fig. 3(b)(right): cerebellar normalisation. The figures illustrate the orthogonal maximum intensity projections of the thresholded statistical parametric map. The map is thresholded at an individual voxel value of 3.09 ($p = 0.001$) and clusters of voxels having a probability of chance occurrence of < 0.001 , when corrected for multiple comparisons, are displayed.

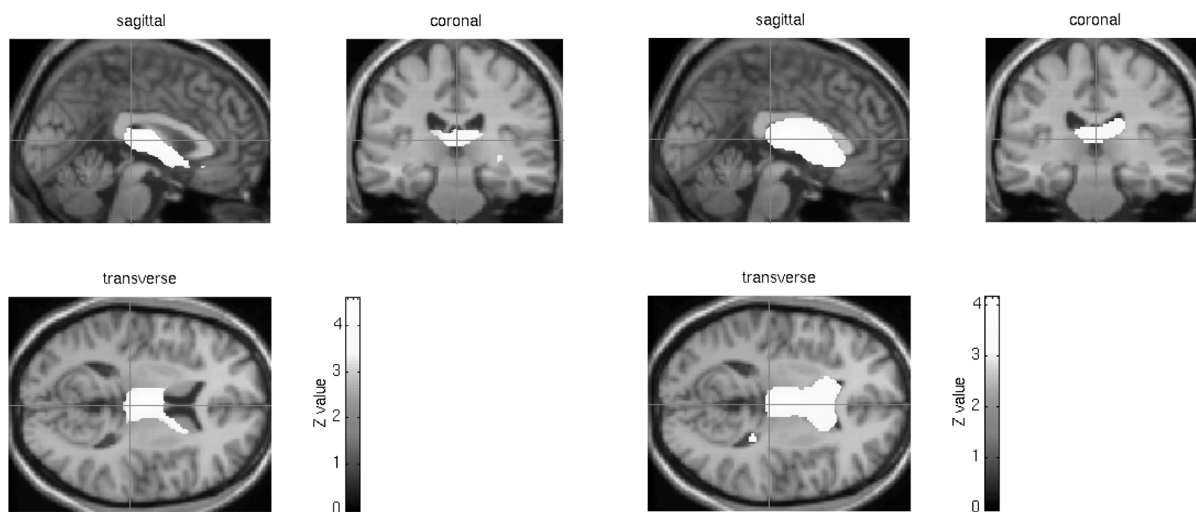


Fig. 4. SPM results comparing the patient group with control subjects; Fig. 4(a)(left): whole brain normalisation, Fig. 4(b)(right): cerebellar normalisation. The figures show selected orthogonal slices through the corresponding statistical parametric map superimposed on a standard T1 weighted MR image, which is displayed in Talairach space.

bance in the 'other' group. This is seen with significant differences between the control group and the 'other' group, but not between the control group and the ACoA group.

6. Discussion

This study clearly demonstrates that patients who undergo surgery for aneurysmal subarachnoid haemor-

rhage are significantly cognitively impaired, even at 12 months post-surgery. This would indicate that these deficits are stable and could represent permanent impairment. Despite the sparing of basic cognitive skills, such as expressive language and concentration, deficits appear to be global with lowered performance on certain IQ tests, all memory tests and many 'executive' tests thought to require the integrity of the frontal lobes.

It is unclear why performance is retained on a small number of tests. Consideration of the nature of those

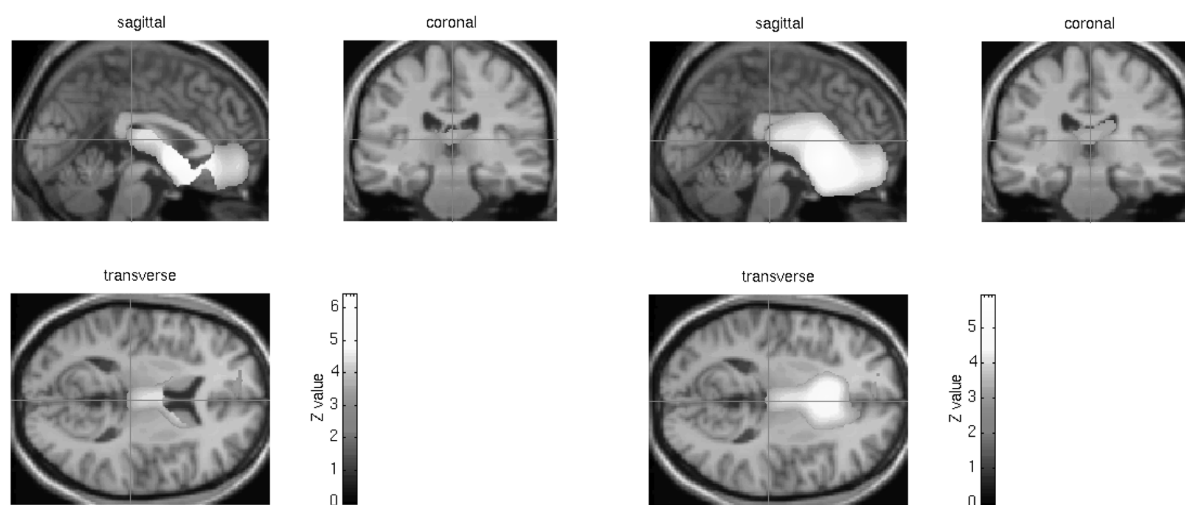


Fig. 5. SPM results comparing ACoA patients with control subjects; Fig. 5(a)(left): whole brain normalisation, Fig. 5(b)(right): cerebellar normalisation. The figures show selected orthogonal slices through the corresponding statistical parametric map superimposed on a standard T1 weighted MR image, which is displayed in Talairach space.

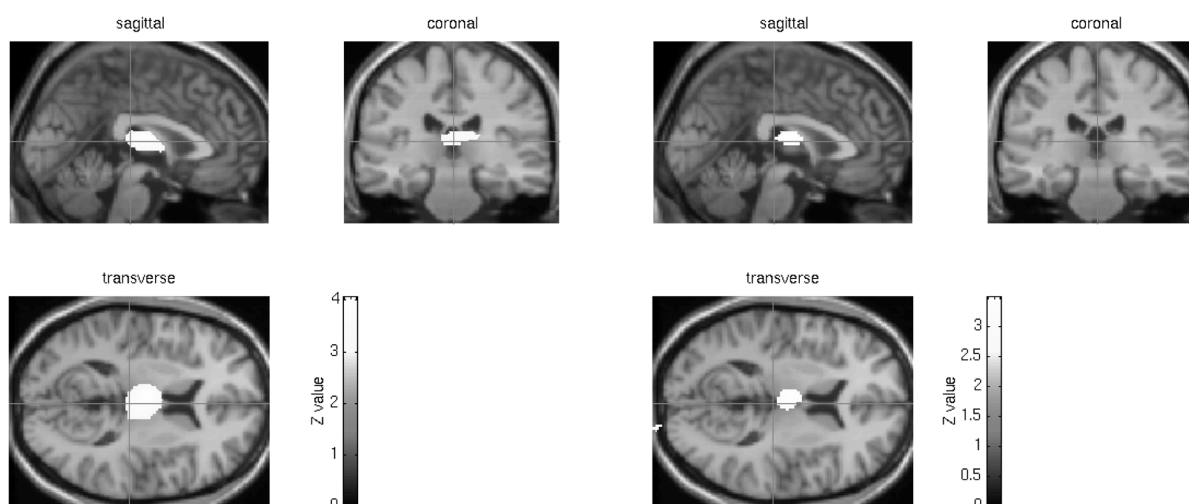


Fig. 6. SPM results comparing patients with aneurysms at sites other than ACoA with control subjects; Fig. 6(a)(left): whole brain normalisation, Fig. 6(b)(right): cerebellar normalisation. The figures show selected orthogonal slices through the corresponding statistical parametric map superimposed on a standard T1 weighted MR image, which is displayed in Talairach space.

tests suggests the hypothesis that patients can benefit from exerting extra effort (reflected in longer time taken to complete) under conditions of external cueing. For example, in the form discrimination task, in which the stimuli remain available to the patient, they were significantly slower but did not make more errors. Similarly, on the spatial working memory task, where the stimuli remain available throughout the task, significant impairment was seen in the strategy score, which must be internally generated, but not in the error score.

The analysis which separated those patients with aneurysms of the ACoA from all other patients failed to demonstrate any significant differences between these 2 groups. This adds to the equivocal literature regarding the nature of ACoA deficits, supporting the emerging view that aneurysm location alone is not sufficient to elicit distinct profiles of cognitive performance. Although differences in affective state were not significant between the two patient groups there was a trend for the ACoA group to show less depression and anxiety.

Table 3
Neuropsychological test results

Test	Mean (standard deviation)			P value		Post hoc analysis		
	HCS	ACoA	'other' aneurysm	HCS/all	HCS/ACoA/ 'other'	HCS/ ACoA/ 'other'	ACoA 'other'	HCS/ 'other'
Intelligence								
Vocabulary	52.2 (8.8)	41.9 (14.5)	43.6 (14.2)	0.0001	0.0002	*	*	
Arithmetic	12.9 (3.5)	10.9 (4.9)	11.8 (4.0)	0.04	0.09			
Similarities	20.7 (4.0)	18.2 (5.7)	19.7 (4.8)	0.05	0.07			
Picture arrangement	13.6 (3.9)	9.5 (5.5)	12.0 (5.0)	0.001	0.0007	*		
Block design	33.7 (9.1)	24.3 (11.3)	27.7 (12.2)	0.0002	0.0004	*	*	
Immediate memory								
Digit span forwards	8.8 (2.2)	8.2 (2.5)	8.0 (2.2)	0.09	0.2			
Digit span backwards	7.6 (2.4)	6.8 (2.2)	7.4 (2.6)	0.3	0.4			
Spatial span (CANTAB)	5.7 (1.5)	5.1 (1.1)	5.4 (1.6)	0.2	0.3			
Memory								
Word recognition	48.4 (2.6)	45.7 (3.7)	46.7 (5.6)	0.003	0.009	*		
Face recognition	46.7 (3.3)	41.4 (6.1)	42.3 (4.7)	0.0000	0.0000	*	*	
Story recall: immediate	11.5 (2.7)	9.5 (2.8)	9.4 (3.4)	0.0003	0.001	*	*	
Story recall: 30 minute delay	10.2 (2.6)	7.1 (3.7)	8.0 (3.5)	0.0000	0.001	*	*	
Complex figure:	0.2 (0.2)	0.5 (0.2)	0.4 (0.3)	0.0000	0.0000	*	*	
% recall of copied design								
Executive								
Tower of London:	66.8 (19.6)	71.7 (13.2)	66.9 (14.4)	0.4	0.4			
% solved in minimum number of moves								
Tower of London: moves above minimum	14.6 (9.4)	11.5 (6.5)	13.9 (5.8)	0.2	0.2			
ID/ED: stages completed	8.4 (1.3)	8.0 (1.3)	7.9 (1.6)	0.1	0.3			
ID/ED: trials to extra-dimensional shift	22.1 (16.1)	24.8 (13.6)	26.2 (12.8)	0.2	0.5			
Trails test: b - a	31.8 (18.5)	50.5 (41.2)	48.9 (28.1)	0.001	0.005	*	*	
Trails test: b / a	2.1 (0.8)	2.2 (0.8)	2.3 (0.6)	0.2	0.3			
Spatial working memory:	27.1 (18.9)	36.6 (17.0)	32.7 (20.9)	0.04	0.08			
between search errors								
Spatial working memory: strategy score	32.6 (5.2)	35.9 (3.4)	35.5 (4.8)	0.0007	0.003	*	*	
Digit ordering	83.8 (12.6)	69.5 (18.3)	72.1 (17.5)	0.0001	0.0002	*	*	
Letter fluency	39.8 (10.3)	28.9 (12.0)	30.3 (11.4)	0.0000	0.0000	*	*	
Semantic + alternating fluency	44.2 (8.0)	29.5 (10.2)	32.1 (9.9)	0.0000	0.0000	*	*	
Language								
Boston: no cue	37.1 (2.1)	36.4 (4.3)	36.1 (4.2)	0.2	0.4			
Boston: semantic cue	37.9 (1.8)	37.2 (3.7)	36.7 (3.8)	0.1	0.2			
Boston: phonemic cue	39.4 (0.8)	38.9 (2.3)	38.8 (1.7)	0.06	0.2			
Visuo-spatial								
Complex figure: copy	17.8 (1.4)	16.6 (2.1)	16.8 (1.8)	0.0008	0.003	*	*	
Form discrimination: accuracy	15.8 (1.2)	15.6 (1.5)	15.6 (1.5)	0.3	0.6			
Form discrimination: speed	47.2 (18.7)	63.0 (34.0)	56.7 (16.3)	0.005	0.01		*	
Affect								
Beck Depression Inventory	5.0 (3.3)	8.2 (8.3)	12.6 (11.5)	0.0002	0.001		*	
POMS total score	16.1 (20.7)	35.5 (48.9)	52.2 (45.2)	0.0001	0.0001		*	
Anger	5.6 (5.0)	8.4 (9.9)	10.4 (8.9)	0.09	0.02		*	
Anxiety	7.3 (4.2)	12.1 (9.3)	16.2 (8.8)	0.0000	0.0001	*	*	
Confusion	6.1 (3.1)	8.8 (7.1)	11.0 (7.6)	0.0007	0.001		*	
Depression	6.9 (5.8)	10.0 (13.4)	14.0 (15.5)	0.02	0.02		*	
Fatigue	7.4 (5.5)	10.0 (7.7)	12.8 (7.3)	0.002	0.002		*	
Vigour	17.2 (5.9)	13.7 (7.3)	12.3 (7.8)	0.001	0.004		*	

HCS: healthy control subjects.

P values in bold indicate those that withstand Bonferroni correction for 37 comparisons.

* indicate a significant difference at $P < 0.05$ according to Tukey's hsd *post hoc* comparison.

As these states are related to lowered performance on many cognitive tasks it is feasible that this could have reduced the differences between the groups. However,

ongoing detailed multifactorial analysis of the cognitive data indicate that differences in affective disturbance are unlikely to be sufficient to cause the obtained

results.

This study has also demonstrated significant differences in subcortical uptake of ^{99m}Tc HMPAO in patients following surgery for subarachnoid haemorrhage, when compared with control subjects. Although the patient group was dominated by the large number of subjects with aneurysms of the anterior communicating artery, (30 out of a total of 62), this is not a feature which is peculiar to one aneurysm site, since central hypoperfusion is also seen when the images from patients with aneurysms at other sites were examined (Figs 3 and 6). The common area of hypoperfusion which exists in these patients at twelve months following surgery, and the lack of statistically significant differences between the patient groups (subdivided according to aneurysm site) with respect to cognitive function, suggests there may be a link between reduced subcortical functioning and the extent and severity of cognitive deficits. There is clear evidence of reduced thalamic uptake of HMPAO in the patients studied, both from the statistical parametric mapping techniques and also from a simple region of interest (ROI) analysis. ROIs over the cerebellum and thalamus in all the subjects in this study showed a highly significant difference in the thalamus:cerebellar uptake ratio in patients compared with control subjects ($p < 0.001$). Interestingly, on MR imaging, there was no evidence of structural damage to the thalamus in the majority of the patients studied.

The reason for the subcortical hypoperfusion is not clear, although there are a number of possible theories. Also, one must consider the possibility of this being a spurious result caused by some anomaly such as poor mapping of a substantially damaged brain onto the Talairach brain, or a flow void caused by something other than hypoperfusion, particularly when the region in question is adjacent to the ventricles and site of the aneurysm. Whilst it is feasible that an aneurysm could cause such a flow void as they do not take up ^{99m}Tc -HMPAO this would only be likely in the case of giant aneurysms, none of which were present in this study. Further, as these scans were 12 months post-surgery they are unlikely to continue to show any patent lumen.

Similarly, a spurious area of hypoperfusion adjacent to the ventricles could be anticipated in patients with hydrocephalus. Although the spatial resolution of SPECT (especially after smoothing for SPM) makes differentiation of ventricular space and white matter difficult it was possible to reject this explanation on the basis of the MR scans, using both clinical inspection and the bicaudate ratio. The bicaudate ratio is an objective measure of ventricular enlargement with nor-

mative age-related values (see [31] for a review). The stated upper limit of normal for 50 years of age is 0.18. Both of the patient groups fell below this upper limit, indicating an absence of ventricular enlargement and consequent spurious region of hypoperfusion (ACoA group: mean = 0.17, standard deviation = 0.05; other aneurysm group: mean = 0.15; standard deviation = 0.04).

Having rejected explanations for a false positive result it is conceivable that it could represent direct damage to the thalamus, either as a result of the haemorrhage itself or the subsequent surgery. In this regard, it is interesting to note that in a study of SPECT brain perfusion imaging in traumatic brain injury [1] over 50% of the sites of hypoperfusion were located in the basal ganglia and thalami. However, the lack of any indication on MR imaging of major structural damage to the thalamus suggests that any direct structural damage to the thalamus would have to be subtle, and that this would in turn need to produce fairly extensive blood flow changes. A second explanation for the subcortical hypoperfusion is that it is secondary to damage elsewhere in the brain. It is possible that the changes which we have demonstrated in the thalamic area on SPECT imaging represent a physiological response to reductions in cortical perfusion. The results could be consistent with a hypothesis of secondary dysfunction of the thalamus, resulting from cortical damage in non-overlapping sites giving rise to a general reduction in thalamic blood flow.

Given that the thalamus is a relay station to many cortical areas, it is conceivable that dysfunction of the thalamus, for whatever reason, could produce global cognitive deficits by reducing output to all parts of the cortex from diffusely projecting thalamic nuclei. The net result of this could be to produce sub-optimal cognitive function even in intact cortical regions. Such a theory could explain our finding of global cognitive impairment in the patient group which does not appear to be associated with aneurysm site. Berry and co-workers [3] obtained similar results in their study of 48 patients who had undergone surgery for aneurysmal subarachnoid haemorrhage. Compared with controls, their patient group as a whole showed a cognitive deficit which was unrelated to medical and surgical variables, including site of aneurysm, which might have been expected to be contributory. Although the patient group studied by these authors underwent SPECT scanning, the results were reviewed on an individual patient basis. SPECT abnormalities were reported to be distributed 'across a wide anatomical area'. This finding is not

inconsistent with our own data on an individual patient basis. However, the lack of any group analysis of the image data by Berry et al may have masked any subtle but consistent subcortical hypoperfusion which may have been present in the group as a whole. Indeed, had our own study not involved a groupwise analysis, it is doubtful whether the thalamic hypoperfusion would have been detected. Thus it is possible that a similar underlying central perfusion deficit could also explain the results of Berry and co-workers.

It is difficult to draw any firm conclusions at this stage on the relationship between subcortical hypoperfusion and cognitive performance in this group of patients. Indeed, the possibility that the reduced thalamic blood flow which we have observed is coincidental and unrelated to cognitive performance cannot be excluded. What is clear is the need for further research in this area. We are currently examining the detailed distribution of structural damage in these patients in relation to aneurysm site and investigating the correlation between severity of cognitive deficit and thalamus to cerebellar uptake ratio in SPECT images of individual subjects. Furthermore, ongoing analyses correlating the extent of cortical hypoperfusion with the thalamus to cerebellar uptake ratio should help to confirm or reject the second of the proposed hypotheses. This data should shed further light on the possible link between thalamic perfusion and cognitive performance following surgery for aneurysmal subarachnoid haemorrhage and indicate the direction of future research.

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