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Subcortical aphasia and neglect in acute stroke: the role of cortical hypoperfusion

A. E. Hillis,[1,3] R. J. Wityk,[1] P. B. Barker,[2] N. J. Beauchamp,[2] P. Gailloud,[2] K. Murphy,[2] O. Cooper[1] and E. J. Metter[1,4]

[1]*Department of Neurology and* [2]*Department of Radiology, Johns Hopkins University School of Medicine,* [3]*Johns Hopkins University Department of Cognitive Science and* [4]*The National Institute on Aging, Baltimore, MD 21287, USA*

Correspondence to: A. Hillis, Department of Neurology, Johns Hopkins Hospital, Meyer 5-185, 600 N. Wolfe Street, Baltimore, MD 21287, USA
E-mail: argye@JHMI.edu

Summary

We have hypothesized that most cases of aphasia or hemispatial neglect due to acute, subcortical infarct can be accounted for by concurrent cortical hypoperfusion. To test this hypothesis, we demonstrate: (i) that pure subcortical infarctions are associated with cortical hypoperfusion in subjects with aphasia/neglect; (ii) that reversal of cortical hypoperfusion is associated with resolution of the aphasia; and (iii) that aphasia/neglect strongly predicts cortical ischaemia and/or hypoperfusion. We prospectively evaluated a consecutive series of 115 patients who presented within 24 h of onset or progression of stroke symptoms, with MRI sequences including diffusion weighted imaging (DWI) and perfusion weighted imaging (PWI), and detailed testing for aphasia or hemispatial neglect. The association between aphasia or neglect and cortical infarct (or dense ischaemia) on DWI and cortical hypoperfusion indicated by PWI, was evaluated with chi-squared analyses. Fisher exact tests were used for analyses with small samples. Cases of DWI lesion restricted to subcortical white matter and/or grey matter structures (n = 44) were examined for the presence of aphasia or neglect, and for the presence of cortical hypoperfusion. In addition, subjects who received intervention to restore perfusion were evaluated with DWI, PWI, and cognitive tests before and after intervention. Finally, the positive predictive value of the cognitive deficits for identifying cortical abnormalities on DWI and PWI were calculated from all patients. Of the subjects with only subcortical lesions on DWI in this study (n = 44), all those who had aphasia or neglect showed concurrent cortical hypoperfusion. Among the patients who received intervention that successfully restored cortical perfusion, 100% (six out of six) showed immediate resolution of aphasia. In the 115 patients, aphasia and neglect were much more strongly associated with cortical hypoperfusion (χ^2 = 57.3 for aphasia; χ^2 = 28.7 for neglect; d.f. = 1; P < 0.000001 for each), than with cortical infarct/ischaemia on DWI (χ^2 = 8.5 for aphasia; χ^2 = 9.7 for neglect; d.f. = 1; P < 0.005 for each). Aphasia showed a much higher positive predictive value for cortical abnormality on PWI (95%) than on DWI (62%), as did neglect (100% positive predictive value for PWI versus 74% for DWI). From these data we conclude that aphasia and neglect due to acute subcortical stroke can be largely explained by cortical hypoperfusion.

Keywords: cerebrovascular disease; stroke; aphasia; hemispatial neglect

Abbreviations: DWI = diffusion weighted imaging; MCA = middle cerebral artery; PWI = perfusion weighted imaging; TTP = time to peak

Introduction

Although aphasia and hemispatial neglect are classically designated as 'cortical' deficits, language deficits or hemispatial neglect following lesions to the basal ganglia, thalamus or other subcortical regions have been reported in many single case reports and case series (Damasio *et al*., 1982; Naeser *et al*., 1982; Megens *et al*., 1992; Ferro *et al*., 1987; Weiller *et al*., 1990; Weiller *et al*., 1993). In addition, data from a large acute stroke trial have shown that aphasia and neglect in acute stroke are only modest predictors of cortical infarct on follow-up CT (Worrall *et al*., 2001). That is, of 221 patients enrolled in this trial, cortical lesions were found in only 55% of patients with acute aphasia (without neglect) and in only 64% of patients with hemispatial neglect (without aphasia). Cortical infarcts were not significantly

associated with either aphasia ($\chi^2 = 1.37$; d.f. = 1; $P = 0.24$) or neglect ($\chi^2 = 0.81$; d.f. = 1; $P = 0.37$). One possible, but controversial, account of these findings is that acute aphasia and hemispatial neglect following subcortical lesions are due to associated cortical dysfunction not visible by CT or conventional MRI (Weiller *et al*., 1993; Nadeau and Crosson, 1997; Démonet, 1997; Craver and Small, 1997; Wallesch, *et al*., 1997). In support of this hypothesis, several studies have shown cortical hypoperfusion in patients with aphasia and/or neglect associated with subcortical stroke, using SPECT (single photon emission computed tomography) (Skyhøj Olsen *et al*., 1986; Vallar *et al*., 1988; Weiller *et al*., 1993). In these studies, acute stroke was evaluated with CT, which is less sensitive to small areas of infarct than MRI. Thus, it is possible that the CT scans might have 'missed' patchy or small cortical infarcts in the acute stage. PET studies that have demonstrated cortical hypometabolism associated with chronic or subacute subcortical lesions (Kuhl *et al*., 1980; Metter *et al*., 1983; Baron *et al*., 1986) and the consistent presence of cortical hypometabolism in essentially all aphasic subjects (Metter *et al*., 1990) support the proposal that subcortical aphasia and neglect are due to cortical dysfunction. In addition, Metter and colleagues reported a case study showing frontal hypometabolism associated with an internal capsule infarction (Metter *et al*., 1985). At autopsy (one week after the imaging study), the internal capsule lesion was associated with white matter degeneration in the anterior limb, while neuronal cell counts in the hypometabolic frontal cortex did not differ from the contralateral cortex.

Until recently, it has been difficult to evaluate the extent of infarct and hypoperfusion in the first 24 h following stroke onset. However, in the past few years, advanced MRI techniques of diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) have made such evaluation possible. DWI is highly sensitive to dense ischaemia or infarct hours after the onset of stroke symptoms, while PWI reveals areas of delayed arrival and clearance of a bolus of contrast, indicating poor perfusion (Barber *et al*., 1998; Beauchamp *et al*., 1999; Fisher and Albers, 1999; Marks *et al*., 1999; Sunshine *et al*., 1999). Although DWI abnormalities are occasionally reversible, they are very sensitive to true infarct, as well as to areas of dense ischaemia that are unlikely to be functional or salvageable. These imaging techniques allow assessment of both the structural lesion and the 'functional lesion' in early stroke.

Subcortical infarction may cause aphasia or neglect either directly or through disruption of subcortical-cortical circuits, or may simply be temporally associated with cortical hypoperfusion that causes aphasia or neglect. We prospectively determined the extent to which aphasia and hemispatial neglect with infarcts restricted to subcortical regions could be accounted for by concurrent cortical hypoperfusion (whether or not due to the subcortical lesion), by studying 115 subjects (44 of whom had only subcortical infarcts) with DWI, PWI, and detailed cognitive testing in the first 24 h of onset or progression of symptoms of acute stroke. We also evaluated whether restoring perfusion to the cortex resulted in resolution of the aphasia in a subset of subjects with aphasia due to subcortical stroke and cortical hypoperfusion. Finally, we determined the positive predictive value of aphasia and neglect for cortical DWI abnormality or cortical PWI abnormality in this acute stroke population.

Methods

Subjects

All patients with the clinical diagnosis of acute, hemispheric stroke, who presented to Johns Hopkins Hospital, Baltimore, MD, USA within 24 h of symptom onset or symptom progression were considered for inclusion. Exclusion criteria were as follows: (i) contraindication for MRI (e.g. implanted ferrous metal, claustrophobia); (ii) allergy to gadolinium; (iii) haemorrhage on initial CT or MRI; (iv) impaired arousal or agitation requiring ongoing sedation; and (v) history of global intellectual deterioration (e.g. dementia). One patient was excluded because she was left-handed and appeared to have right hemisphere dominance for language on the basis that she had a large left middle cerebral artery stroke (MCA) and no language deficits, but severe right hemispatial neglect. Informed consent was obtained according to the Helsinki Declaration using consent forms and the consent process approved by the Joint Commission on Clinical Investigation, the Institutional Review Board at Johns Hopkins University School of Medicine. In patients with impaired language comprehension, informed consent was provided by identified decision-makers (the closest living relative of each patient).

A total of 115 patients, including 80 patients with left hemisphere stroke and 35 patients with right hemisphere stroke, were enrolled. The age of subjects ranged from 23 to 86 years, with a mean of 61 years (SD = 14.8). The time post-onset or worsening of symptoms was 0.5–24 h, with a mean of 10.3 h (SD = 8.4). There were 61 female and 53 male subjects.

Test battery

Patients with left hemisphere stroke were given a bedside battery to evaluate the various levels of representations and processes underlying lexical tasks such as auditory and reading comprehension, picture naming, tactile naming, oral reading and repetition. The tests included: (i) Oral and written naming of pictured objects ($n = 34$ items). (ii) Oral naming of objects with tactile input ($n = 17$ items). (iii) Oral reading of words ($n = 34$) and pseudowords ($n = 25$). (iv) Spelling to dictation of words ($n = 34$) and pseudowords ($n = 25$). (v) Spoken word/picture verification ($n = 51$ items). For this task, each picture was presented once with a semantically related foil (e.g. cake/pie), once with a phonologically related foil (e.g. cake/snake) and once with the correct word (cake/cake) in random order, and the patient was asked to verify

correspondence between the picture and the word. (vi) Written word/picture verification with semantic and visual foils and correct matches, as described above (n = 51 items). (vii) Repetition of words (n = 34) and pseudowords (n = 25). (viii) Discrimination of spoken words versus pseudowords ('lexical decision'). (ix) Spoken yes/no questions (five syntactically complex, five syntactically simple sentence structures) with no contextual cues to assist comprehension of the questions (e.g. Are limes red?). (x) Description of the 'cookie theft' picture from the Boston Diagnostic Aphasia Examination (Goodglass and Kaplan, 1972). Descriptions were scored by a trained speech–language pathologist for number of correct content units, content units/minute and syllable/minute, and compared with published norms (Yorkston and Beukelman, 1980). This test was included only to detect patients who showed evidence of aphasia in spontaneous speech, despite normal performance on the lexical tasks (tests i–viii) and sentence comprehension. No patients met this description.

Word and object stimuli in tests i–viii were matched across tasks for semantic category, familiarity, frequency, grammatical word class and length. Liberal scoring of pseudoword spelling and pronunciation was used. Aphasic subjects who received intervention to restore perfusion to the cortex were administered different forms of this battery before and after treatment. The word stimuli in the two forms were matched for frequency, familiarity, word length in letters and syllables, and word class. For the yes/no questions, the two forms had questions with identical syntactic structures. Questions differed by content words that were matched in word length, frequency and familiarity (e.g. Are lemons white? Are lemons black?).

Patients with right hemisphere stroke were given a battery of bedside tests to evaluate for hemispatial neglect at various levels of spatial representation. Tests included:

(i) Oral reading and oral spelling of lists of frequency-matched and length-matched words and pseudowords (e.g. samp). Patients who made errors restricted to one side of the word (neglect errors) in reading standard print were presented with matched lists of word stimuli in mirror-reversed print and vertical print [see Hillis and Caramazza (1995) for details of these stimuli].

(ii) Perceptual tasks in which 30 circles and 30 circles embedded in squares are presented. Ten circles have a gap on the left side; 10 have a gap on the right; and 10 have no gap. All stimuli are presented three times, once directly in front of the subject; once on the subject's left (at 45°) and once on the subject's right. Patients report 'gap' or 'no gap' in each condition (described by Hillis and Selnes, 1999).

(iii) Perceptual motor tasks, including: line cancellation; the Bells Test (Gauthier *et al*., 1989); and copying the 'Ogden scene' (a house, a fence and two trees) once with the scene right side up and once with the scene rotated 180°.

(iv) Motor tasks to test motor extinction, in which patients without hemiplegia were asked to click a golf counter with each hand, as quickly as possible for 1 min. The clicking rate was tested in three conditions: (i) each hand independently; (ii) the two hands simultaneously, with the hands at the subject's sides; and (iii) the two hands simultaneously, with arms crossed across the chest (to distinguish impaired clicking with the left relative to the right hand versus impaired clicking on the left versus the right side of the midsagittal plane of the body (Hillis *et al*., 1998).

Norms were obtained for the language and neglect battery by administering each battery to 46 volunteer control subjects who were awaiting surgical repair of unruptured intracerebral aneurysms or awaiting cardiac bypass surgery. These controls were not only comparable in age, education and sex ratio to the stroke patients, but also had similar health problems (except acute stroke). For subjects and controls whose highest education was below tenth grade or who reported premorbid impairment of reading or writing, the reading and writing subtests were not scored. Mean scores for each subtest ranged from 98.0% (SD = 3.1) correct in oral reading to 100% (SD = 0) correct in tactile naming. Abnormal performance was defined as 89% correct or lower; normal performance was defined as 90% correct or higher. This cut-off was selected because 89% was three standard deviations below the mean on the subtest with the lowest mean. No control subject scored below 90% correct on any subtest of the battery. Patients were considered to have aphasia or neglect if they scored below 90% correct on any one or more of the subtests.

The language and spatial attention batteries were administered by a trained neuropsychology technician or speech–language pathologist. The inter-rater reliability in scoring 12 selected batteries was >95% point-to-point agreement for each subtest.

Imaging protocol

The following MRI sequences were obtained: sagittal T_1-weighted localizer images; axial DWI, spin-echo, FLAIR (fluid attenuated inversion recovery) and T_2-weighted images; and GdDTPA (gadolinium) PWI on a GE Signa 1.5 tesla, echo planar imaging capable system (General Electric Medical Systems, Milwaukee, WI, USA). DWI trace images were obtained using a multi-slice, isotropic, single shot EPI (echoplanar imaging) sequence, with b_{max} = 1000 s/mm^2. Imaging parameters were TR (relaxation time) = 10 000 ms and TE (echo time) = 120 ms. For PWI, single shot gradient echo EPI perfusion images (TR/TE of 2000/60 ms) were obtained with 20 cm^3 GdDTPA bolus power injected at 5 cm^3/s. This gradient echo sequence allows 17 slices to be recorded with a 2 s repetition rate.

The presence or absence of cortical hypoperfusion was identified by a trained technologist and neuroradiologist blinded to the results of functional testing. Regions of hypoperfusion were delineated by analysis of 20-colour time-to-peak (TTP) maps, in which each colour change corresponds to a 2.5 s difference in delay in TTP concentration of tracer in each pixel, using the Scion Image program (1998

version) (Scion Corporation, Frederick, MD, USA). Hypoperfusion was defined as >2.5 s delay compared with the homologous region in the other hemisphere. This threshold was based on an earlier study in which we found that >2.5 s delay in TTP in Wernicke's area relative to the homologous region in the intact hemisphere was associated with language dysfunction characteristic of that area (Hillis *et al*., 2001*c*), and on a previous study indicating that the volume of abnormality on PWI correlated with the severity of dysfunction when a threshold of >2 s relative delay in TTP was selected (Neumann-Haefelin *et al*., 1999). There was 100% point-to-point percentage agreement between the neuroradiologist and the technician in identifying the presence or absence of cortical hypoperfusion. Sites of dense ischaemia or infarct were identified on DWI trace images [with corresponding absolute diffusion coefficient (ADC) maps] co-registered to T_2-weighted images (with better spatial resolution) by a neuroradiologist blinded to the results of the cognitive testing.

Data analyses

The association between aphasia or hemispatial neglect and cortical hypoperfusion in patients with infarcts restricted to specific subcortical regions was evaluated using two by two tables and the Fisher exact test. Similarly, the association between aphasia or hemispatial neglect and cortical infarct was calculated using the Fisher exact test. The positive predictive value of aphasia for DWI abnormality versus PWI abnormality was then determined. Additionally, the positive predictive value of hemispatial neglect for DWI abnormality versus PWI abnormality was determined.

Intervention

A subset of six subjects with subcortical infarcts and cortical hypoperfusion had intervention to restore perfusion. Intervention consisted of induced blood pressure elevation with intravenous phenylephrine ($n = 4$) (for discussion of the rationale and evidence for this intervention, see Wise *et al*., 1972; Rordorf *et al*., 1997; Hillis *et al*., 2001*a*, *b*), urgent carotid endarterectomy ($n = 1$) or carotid stenting ($n = 1$). Subjects had repeat MRI scans (the identical protocol) and repeat cognitive testing the morning after intervention, which was 3 days after the initial scans and cognitive testing. For comparison, one subject with aphasia due to subcortical infarct and cortical hypoperfusion who received no specific intervention to restore perfusion also had repeat testing and repeat imaging at 3 days.

Results

Aphasia and subcortical lesions

For the first analysis, we selected only those subjects whose lesions were restricted to the subcortical white matter, basal ganglia or thalamus. There were 37 patients with exclusively left hemisphere subcortical lesions. Of these 37 with left subcortical lesions, 25 (68%) had aphasia and all had cortical hypoperfusion. In all cases, the hypoperfusion was in the cortex supplied by the left MCA. That is, 100% of the cases in our sample of language deficits associated with isolated subcortical lesions could be accounted for by cortical hypoperfusion in the left MCA territory. Only one of the 12 subjects with left subcortical lesions without aphasia had cortical hypoperfusion; this patient showed hypoperfusion restricted to the occipital cortex. The most common sites of subcortical infarct were corona radiata, caudate or thalamus. Aphasia and cortical hypoperfusion associated with these sites were examined separately. There were 19 subjects with lesions limited to the left corona radiata (white matter); the 16 cases with aphasia all had hypoperfusion of the adjacent cortex and none of the three non-aphasic subjects had cortical hypoperfusion (Fisher exact: $P < 0.00001$). The greater number of aphasic compared with non-aphasic subjects with left corona radiata lesions might influence the statistical results; so these results should be interpreted with some caution. Similarly, there were nine subjects with left caudate infarcts without cortical infarct; the six cases with language deficits all had hypoperfusion of the adjacent left perisylvian cortex and the non-aphasic subjects did not have cortical hypoperfusion *(*Fisher exact: $P = 0.01$). Fig. 1 (*top*) shows the DWI and PWI scans of a subject with hyperacute Wernicke's aphasia due to a left caudate infarct seen on DWI and hypoperfusion of Brodmann area (BA) 22 and BA 37 (dark on PWI). Fig. 1 (*bottom*) shows a subject with normal language performance in the presence of left caudate infarct and no cortical hypoperfusion. Only five subjects had isolated left thalamic infarcts; none of these had identified language impairments. It is possible that they (or patients with other subcortical lesions) had language deficits that were not identified with our battery, which focused on lexical tests. Nevertheless, of the five subjects with thalamic lesions, the only one with cortical hypoperfusion had diminished perfusion of the left occipital cortex and associated visual deficits.

Hemispatial neglect and subcortical lesions

There were 14 patients with lesions restricted to the right subcortical white matter, basal ganglia or thalamus. Of these 14 patients with exclusively right subcortical lesions, seven (50%) had left hemispatial neglect. All these seven patients had cortical hypoperfusion and all seven of the subjects without hemispatial neglect showed no cortical hypoperfusion (Fisher exact: $P < 0.001$). There were seven right caudate/capsular lesions and seven right corona radiata infarcts. For both sites, about half of the patients (four or three, respectively) had left hemispatial neglect (on one or more of the subtests of the spatial attention battery), which could be accounted for by associated cortical hypoperfusion in the distribution of the right MCA in each case (Fisher

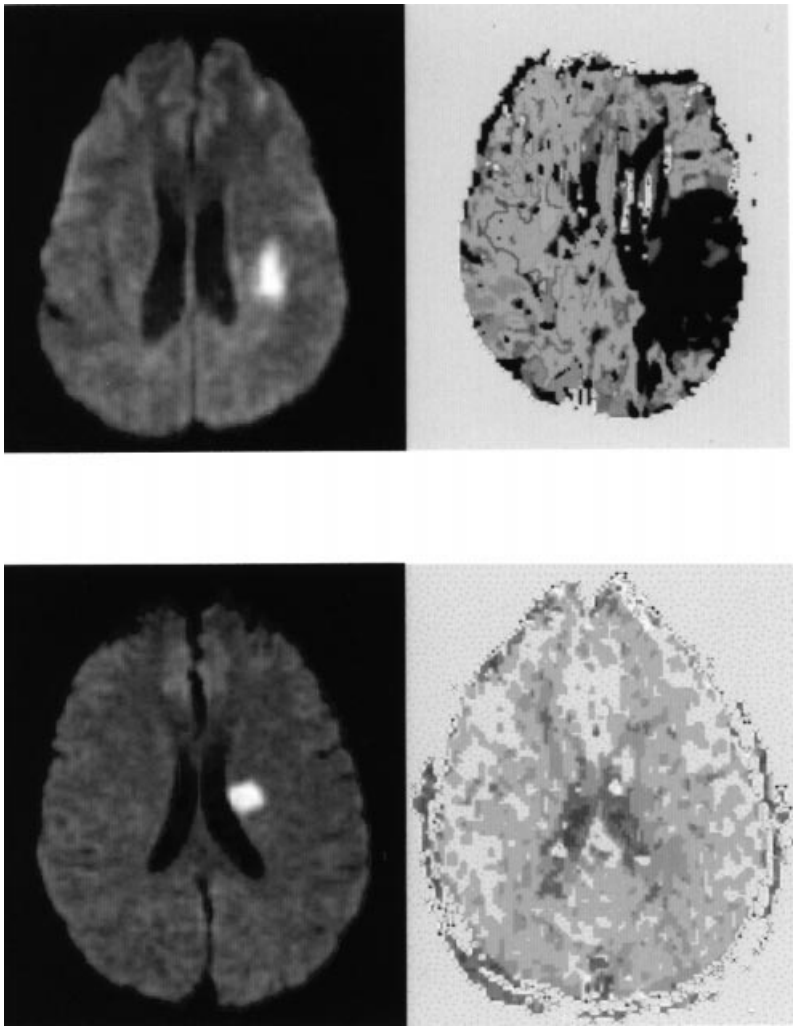

Fig. 1 Left subcortical infarcts with cortical hypoperfusion (*top*) and without cortical hypoperfusion (*bottom*). DWI scans are shown on the left; PWI scans are shown on the right. Hypoperfused regions appear dark.

exact: $P = 0.03$). Illustrative cases of right caudate lesions are shown in Fig. 2. The patient in Fig. 2 with associated cortical hypoperfusion had hemispatial neglect (*top*), whereas the patient in Fig. 2 (*bottom*), who showed normal perfusion of the cortex, had no evidence of hemispatial neglect.

Intervention to restore perfusion

The subset of six subjects with subcortical infarct and cortical hypoperfusion who received intervention to restore perfusion all showed at least partial reperfusion of the cortex on repeat PWI (and no development of cortical infarct by day three; Fig. 3). Repeat cognitive testing at 3 days after symptom onset showed substantial improvement of language, with full recovery in most cases, as shown in Fig. 4. Scores on specific subtests are reported in Table 1. In contrast, one subject had no specific intervention to restore perfusion, but had repeat MRI protocol and repeat cognitive testing at 3 days. He showed persistent cortical hypoperfusion and persistent aphasia ('control' in Table 1).

Aphasia or neglect and cortical abnormalities on MRI

All 115 subjects were included in the last set of analyses. The numbers of subjects with right and left hemisphere stroke (with and without cortical abnormalities) are shown in Table 2.

Of the 80 subjects with left hemisphere stroke, 65 (85%) had significant language deficits (>10% errors on one or more of tasks 1–9 on the language battery). In these 65 subjects, DWI showed only a subcortical abnormality in 25 (38%). In contrast, PWI showed cortical hypoperfusion in 62 (95%) of subjects with lexical deficits. Only three subjects had lexical

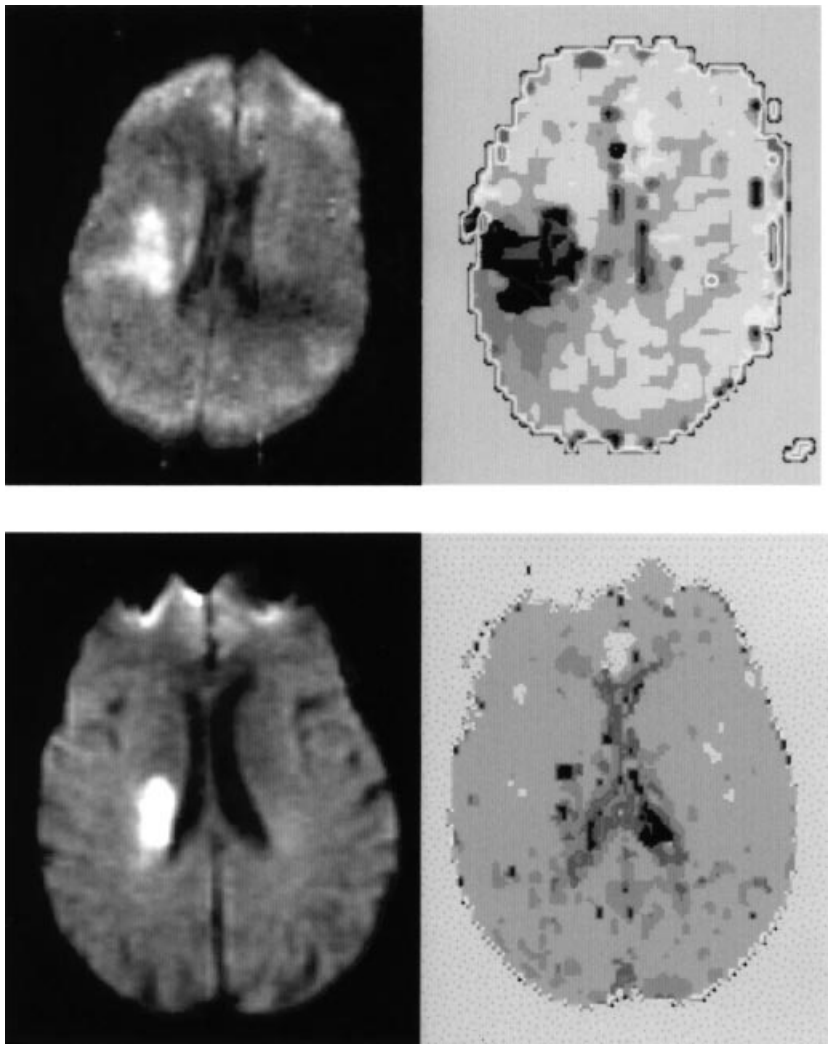

Fig. 2 Right subcortical infarcts with cortical hypoperfusion (*top*) and without cortical hypoperfusion (*bottom*). DWI scans are shown on the left; PWI scans are shown on the right.

deficits with normal cortical perfusion (see Table 3). Each of these three subjects had a cortical lesion and 'luxury perfusion' of infarcted tissue. One subject had hypoperfusion of the left occipital cortex with no lexical deficits (but marked visual deficits).

Similarly, of the 35 patients with right hemisphere stroke, 27 (77%) showed left hemispatial neglect (>10% spatially specific errors on at least one subtest) on the neglect battery, and each of these 27 patients with neglect had cortical hypoperfusion on PWI (Table 3).

Prediction of cortical infarct versus cortical hypoperfusion

Aphasia was significantly associated with cortical infarct ($\chi^2 = 8.5$; d.f. = 1; $P < 0.005$), but much more strongly associated with cortical hypoperfusion ($\chi^2 = 57.3$; d.f. = 1; $P < 0.000001$) in this large sample of acute stroke patients. Similarly, hemispatial neglect was significantly associated with cortical infarct ($\chi^2 = 9.7$; d.f. = 1; $P < 0.001$), but much more strongly associated with cortical hypoperfusion ($\chi^2 = 28.7$; d.f. = 1; $P < 0.000001$) in patients with acute right hemisphere stroke.

The positive predictive value of aphasia and neglect for evaluating cortical infarct and/or cortical hypoperfusion is shown in Fig. 5. Clearly, the presence of aphasia or neglect is an excellent predictor of cortical abnormality, but not a strong predictor of cortical infarct on DWI.

Discussion

This study indicates that many, if not all, cases of aphasia or hemispatial neglect that result from infarcts restricted to subcortical regions can be accounted for by associated cortical hypoperfusion, at least in the acute phase. This argument is based on three findings reported here. First,

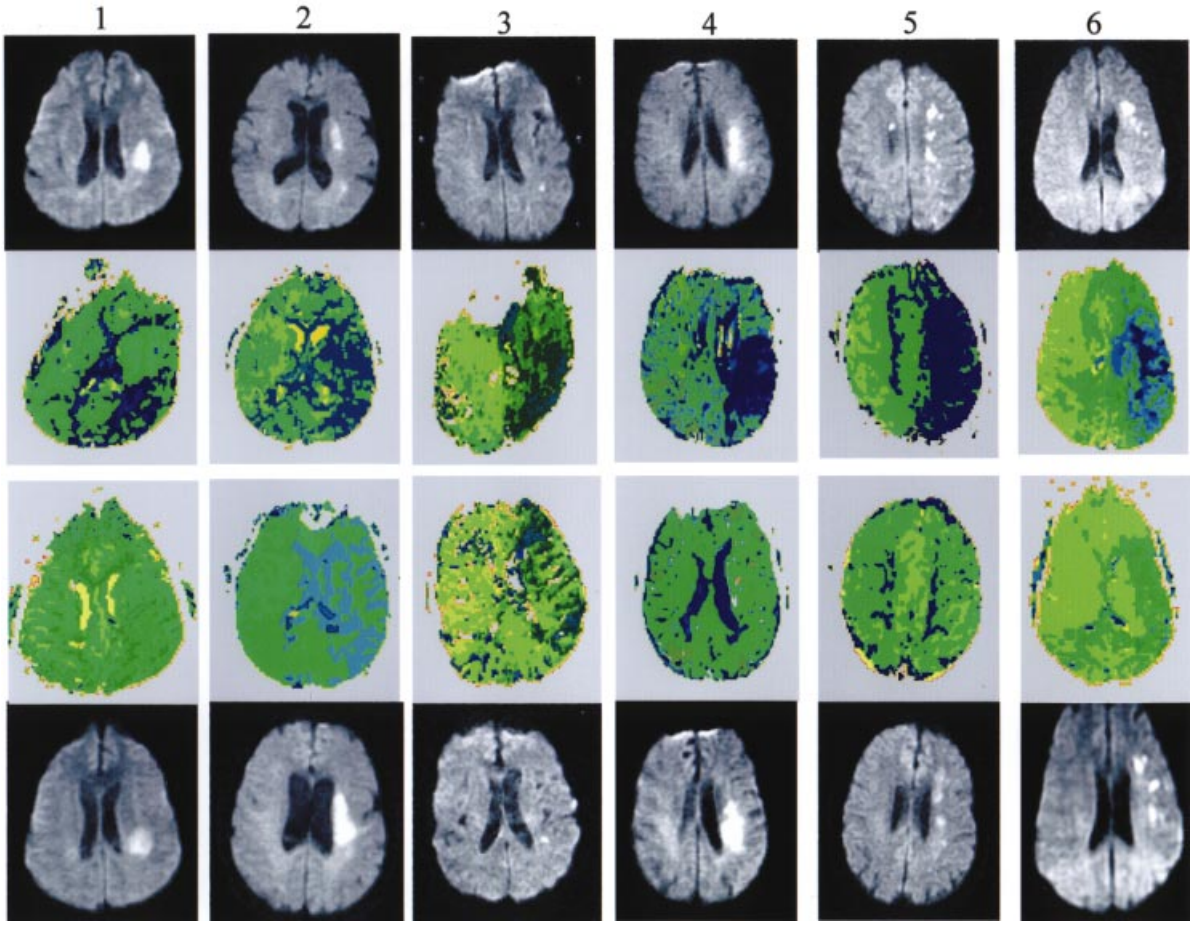

Fig. 3 Baseline (top two rows) and follow-up scans (lower two rows) of subjects with subcortical infarct who showed recovery of language deficits after reperfusion of the left cortex. DWI scans are shown in rows 1 and 4. PWI scans are shown in rows 2 and 3. Each column represents one subject. Hypoperfused regions appear blue.

subcortical infarctions with aphasia and neglect were consistently associated with cortical hypoperfusion (in the MCA territory). Secondly, with reversal of the cortical hypoperfusion, the subjects showed resolution of their aphasic deficit. Thirdly, the presence of aphasia or hemispatial neglect in acute stroke was an excellent marker of cortical dysfunction, consistent with traditional teaching of neurology. However, these 'cortical deficits' were found to be only modest markers of cortical infarct. Although some cases of subcortical infarct with cortical hypoperfusion progress to cortical infarction, many do not. Our results are consistent with the findings of Skyhøj Olsen and colleagues (Skyhøj Olsen *et al*., 1986), who reported that five aphasic subjects with subcortical infarcts (by CT) had low cortical regional cerebral blood flow (rCBF), whereas five nonaphasic subjects with subcortical infarcts had normal cortical rCBF measured by intracarotid injection technique with SPECT at 1–4 days after stroke onset. Although TTP maps on PWI (used in our study) do not strictly show 'perfusion' (but rather show the time to peak arrival of contrast to each voxel of the image), TTP maps can estimate the areas of dysfunction due to hypoperfusion (Hillis *et al*., 2001*c*). Thus, our results confirm the basic conclusions of Skyhøj Olsen and colleagues. Similar findings in subacute or chronic stroke have been reported by others (Perani *et al*., 1987; Vallar *et al*., 1988; Weiller *et al*., 1990, 1993; dela Sayette *et al*., 1992) using CT and SPECT (and follow-up MRI in a subset of subjects) (Weiller *et al*., 1990). In these studies, the initial CT scan might have missed patchy or small cortical infarcts that could cause aphasia or neglect. However, in the present study, we were able to evaluate for cortical infarcts with DWI, which is highly sensitive to infarct within hours of stroke onset (Sunshine *et al*., 1999). We confirmed that even in cases where the infarct or dense ischaemia was restricted to subcortical tissue (by DWI), aphasia or neglect was usually present when there was concurrent cortical hypoperfusion. As in the previous smaller studies, we found that 100% of subjects with aphasia or neglect showed cortical hypoperfusion in the MCA distribution. Similarly, studies in more chronic aphasias examining glucose metabolism with PET have noted the consistent metabolic involvement of cortical temporoparietal regions in essentially all subjects (Metter *et al*., 1990). Even in cases of left hemispheric

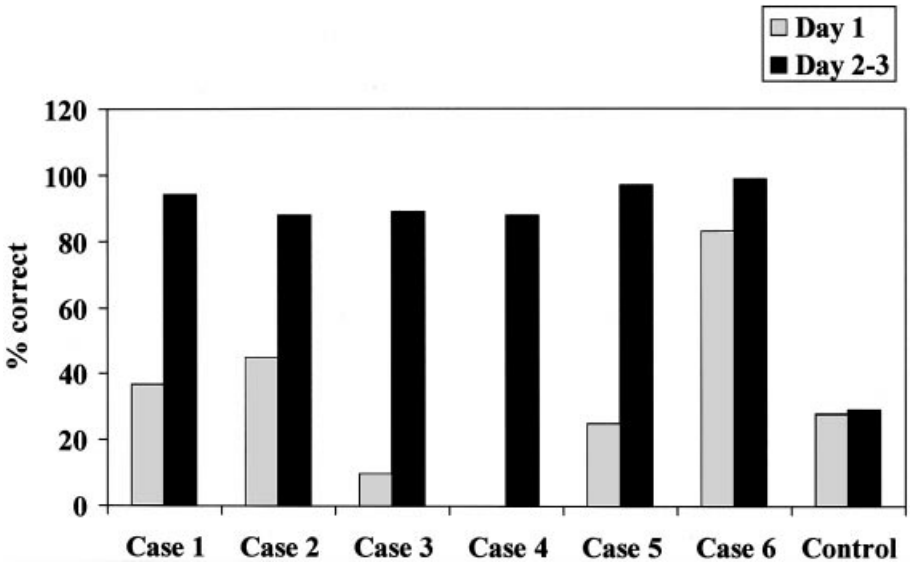

Fig. 4 Pre- and post-intervention total scores on the language battery for six subjects and one control.

Table 1 *Pre- and post-intervention percentage correct on selected subtests of the language battery*

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Control
Pre-intervention (%)							
Oral naming: pictures	0	6	0	0	0	88	0
Oral naming: tactile	0	19	0	0	47	88	24
Written naming	nd	12	nd	nd	0	35	0
Spoken word/picture	47	74	40	0	53	100	54
Written word/picture	nd	76	nd	nd	47	100	0
Repetition	100	80	0	0	0	88	88
Post-intervention (%)							
Oral naming: pictures	94	82	88	76	100	100	0
Oral naming: tactile	88	88	78	100	100	100	29
Written naming	nd	65	nd	nd	100	94	0
Spoken word/picture	94	98	88	76	100	100	59
Written word/picture	nd	100	nd	nd	100	100	0
Repetition	100	95	100	100	84	100	88

*nd = not determined due to premorbid reading/writing difficulty or illiteracy.

Table 2 *Subjects with cortical infarct and/or hypoperfusion*

	DWI abnormality	PWI abnormality
Left hemisphere abnormalities (n = 80)	43	63
Right hemisphere abnormalities (n = 35)	21	28

haemorrhages studied during the chronic phase with PET, cortical hypometabolism has been demonstrated in the aphasic subjects (Metter *et al*., 1986). In this study, CT scans of the chronic aphasic subjects suggested some cortical atrophy (mostly splaying of the Sylvian fissure) but not infarction.

One proposed account of subcortical aphasia or neglect is the presence of diaschisis or physiological dysfunction of a brain region caused by damage to a remote site that is connected via fibre tracts (for review, see Feeney and Baron, 1986; Perani *et al*., 1987; Vallar *et al*., 1988; Wallesch *et al*., 1997). In fact, Metter (1987) argued that there were several patterns of diaschisis (referred to as remote effects) that may have different behavioural implications. However, Nadeau and Crosson (1997) argue against this account of non-thalamic subcortical aphasia on the basis that if diaschisis were the mechanism, similar lesions should produce consistent symptoms. In contrast with this prediction, similar lesions

Table 3 *Relationship between aphasia or neglect and abnormalities on DWI and PWI*

	DWI		PWI	
	Cortical infarct	No cortical infarct	Cortical hypoperfusion	No cortical hypoperfusion
Left hemisphere stroke				
Aphasia	40	25	62	3
No aphasia	3	12	1	14
χ^2	8.5; $P < 0.005$		57.3; $P < 0.000001$	
Right hemisphere stroke				
Neglect	20	7	27	0
No neglect	1	7	1	7
χ^2	9.7; $P = 0.001$		28.7; $P < 0.00001$	

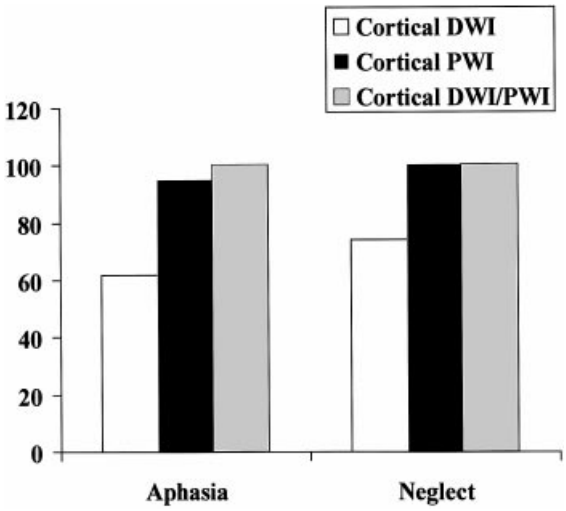

Fig. 5 Positive predictive value of aphasia and neglect for cortical DWI abnormality (dense ischaemia or infarct), cortical PWI abnormality (hypoperfused tissue indicated on TTP map) and cortical DWI and/or PWI abnormality.

(e.g. striatocapsular infarction involving the head of the caudate, putamen and anterior limb of the internal capsule) produce a wide variety of language disturbances or no language deficits at all (Weiller *et al*., 1990; Alexander *et al*., 1997; Nadeau and Crosson, 1997). Furthermore, Weiller and colleagues found that all of their subjects who had aphasia or neglect due to striatocapsular infarct had occlusion of the M1 segment of the MCA by angiogram. All subjects who showed rapid recanalization of the MCA, or who had excellent leptomeningeal anastomoses, showed no aphasia or neglect. These findings are consistent with the view that cortical hypoperfusion (due to vascular occlusion) was the cause of aphasia or neglect. Baron and colleagues (Baron *et al*., 1986) and Vallar and colleagues (Vallar *et al*., 1988) also showed that improvement in cortical hypometabolism or blood flow after subcortical stroke was associated with recovery from neglect or aphasia, although it was not clear which caused the other. Our study included only patients in the acute phase and excluded cases with subcortical haemorrhage in which cortical hypoperfusion might have been explained by diaschisis. Thus, in our study, it is impossible to determine with certainty whether cortical hypoperfusion was due to vascular stenosis with ischaemia, diaschisis or other focal dysfunction. Our finding that reperfusion of the cortex (brought about by carotid endarterectomy, carotid stenting or pharmacological blood pressure elevation) led to immediate improvement of language function, favours the ischaemic hypothesis at least in our treated patients.

Given the small number of subjects who showed reperfusion of the cortex in this study, we cannot dismiss the possibility that cortical reperfusion sometimes occurs without resolution of the aphasia or neglect, resulting in chronic 'subcortical aphasia' or 'subcortical neglect.' In at least some such cases, it is likely that there has been damage to the cortex due to the period of hypoperfusion, which may not be visible on CT or MRI. Thus, although cortical hypoperfusion could fully account for all cases of acute aphasia or neglect with subcortical infarcts in this study, we cannot rule out the possibility that diaschisis or inapparent damage to the cortex plays a role in some cases. We also cannot exclude the possibility that subcortical lesions can directly cause language deficits (as argued by Damasio *et al*., 1982; and modelled by Metter *et al*., 1988) or hemispatial neglect (Watson *et al*., 1981), although we found no support for this hypothesis in this study of acute stroke. Evidence that the thalamus (particularly the intralaminar nucleus and pulvinar) either directly or indirectly participates in language and spatial attention comes from lesion studies in both animals and humans (Orem *et al*., 1973; Watson *et al*., 1981; Henderson *et al*., 1982; Baron *et al*., 1986) and functional imaging (Friston *et al*., 1993). For instance, reported cases of aphasia or hemispatial neglect consequent to stereotactic lesions to the thalamus (Adrianopoulos *et al*., 1981; Perani *et al*., 1987; Vilkki *et al*., 1984; Velasco, 1986; Hillis *et al*., 1998) are unlikely to be explained by cortical hypoperfusion. Baron and colleagues reported that, in 55 patients with thalamic lesions (including 11 lesions due to stereotactic thalamotomy), the magnitude of neuropsychological impairment was positively correlated with the degree of ipsilateral cortical hypometabolism (on PET) (Baron *et al*., 1992).

Nadeau and Crosson (1997) argued that thalamic lesions disrupt networks or pathways with cortical as well as subcortical components, resulting in cortical dysfunction via diaschisis. They reported that, unlike lesions of the basal ganglia, lesions to specific nuclei of the left thalamus produce relatively consistent language disturbances—as would be expected if the mechanism were diaschisis. Similarly, it seems likely that at least some cases of white matter infarct disrupt axons of cortical neurones, resulting in cortical dysfunction without cortical hypoperfusion. It is plausible that both hypoperfusion and diaschisis may co-exist even in the acute stage of stroke. Nevertheless, our results indicate that cortical hypoperfusion is an important contributor to language deficits and hemispatial neglect in patients with acute subcortical stroke.

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