Re-examining the brain regions crucial for orchestrating speech articulation

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Summary

A traditional method of localizing brain functions has been to identify shared areas of brain damage in individuals who have a particular deficit. The rationale of this 'lesion overlap' approach is straightforward: if the individuals can no longer perform the function, the area of brain damaged in most of these individuals must have been responsible for that function. However, the reciprocal association, i.e. the probability of the lesion causing the deficit, is often not evaluated. In this study, we illustrate potential weaknesses of this approach, by re-examining regions of the brain essential for orchestrating speech articulation. A particularly elegant and widely cited lesion overlap study identified the superior part of the precentral gyrus of the insula (in the anterior insula) as the shared area of damage in chronic stroke patients with 'apraxia of speech', a disorder of motor planning and programming of speech. Others have confirmed that patients with apraxia of speech commonly have damage to the anterior insula. However, this reliable association might reflect the vulnerability of the insula to damage following occlusion or narrowing of the middle cerebral artery (which can independently cause apraxia of speech and many other deficits). To evaluate this possibility, we examined the relationship between apraxia of speech and the insula in three unique ways: (i) we determined the probability of the lesion causing the deficit, as well as the deficit being associated with the lesion, by examining speech articulation and advanced MRIs in two consecutive series of patients with acute left hemisphere, non-lacunar stroke, 40 with and 40 without insular damage; (ii) we studied patients at stroke onset to identify the deficit before it resolved in cases of small stroke; and (iii) we identified regions of dysfunctional brain tissue, as well as structural damage. Using this approach, we found no association between apraxia of speech and lesions of the left insula, anterior insula or superior tip of the precentral gyrus of the insula. Instead, in patients with and without insular lesions, apraxia of speech was associated with structural damage or low blood flow in left posterior inferior frontal gyrus. These results illustrate a potential limitation of lesion overlap studies, and illustrate an alternative method for identifying brain–behaviour relationships.

Introduction

Speech production is a complex process that requires translating a representation of each word's pronunciation into an intricate programme of movements of the lips, tongue, jaw, soft palate, vocal folds and respiratory system. Focal brain damage, such as stroke, can cause a disorder in this orchestration of movements, sometimes known as 'apraxia of speech'. Apraxia of speech is one of many impairments of speech and language that can be caused by focal brain lesions.

It is manifest by distortions of consonants, vowels and prosody, that may be perceived as sound substitutions and mis-assignments of stress, and occurs in the absence of reduced strength or tone of muscles of the speech articulators (lips, tongue, jaw and palate) or muscles controlling phonation (McNeil *et al.*, 2000). The person with apraxia of speech knows what he or she wants to say and how it should sound, but cannot accurately programme the articulators to

make the desired sounds. In 1865, Paul Broca reported that autopsies of patients with impaired speech articulation (though not specifically apraxia of speech) showed damage to the left posterior inferior frontal gyrus (Broca, 1865). This area has since come to be known as Broca's area. More recent studies of CT scan lesions in patients with dyspraxic, effortful speech articulation have shown involvement of Broca's area (Mohr *et al.*, 1978) or Broca's area in combination with other lesions including the insula (Ruff and Arbit, 1981; Schiff *et al.*, 1983). However, this lesion–deficit association has been challenged by recent studies reporting that the most frequent area of damage in patients with apraxia of speech is the left anterior insula (Shuren, 1993; Donnan *et al.*, 1997; Nestor *et al.*, 2003). In fact, a particularly elegant and widely cited investigation showed that the region of 100% overlap in CT or MRI lesions of 25 patients with chronic apraxia of speech (1–14 years after stroke) was the superior tip of the left precentral gyrus of the insula, within the anterior insula (Dronkers, 1996). This finding has led to the conclusion that regions within the anterior insula are essential for speech articulation (e.g. Wise *et al.*, 1999). However, in the study of Dronkers (1996), all of the patients with apraxia of speech had this deficit at least 1 year after stroke, and thus probably had relatively large strokes (since apraxia of speech due to small lesions recovers rapidly; Mohr, 1978; Marien *et al.*, 2001). One problem with lesion overlap studies is that the area of greatest overlap among large strokes may simply reflect the vulnerability of particular regions to ischaemia, due to the distribution of blood flow from the cerebral vessels. For example, a recent study of a consecutive series of 33 strokes due to occlusion of the middle cerebral artery (MCA) demonstrated that 94% of these strokes included damage to the insula (as well as many other areas; Finley *et al.*, 2003). It has also been observed that chronic apraxia of speech is usually caused by large strokes due to narrowing or occlusion of the left MCA (which cause many other deficits as well; Blumstein, 1991). Therefore, we hypothesized that the association between chronic apraxia of speech and insular damage is an artefact of the coincident associations between (i) insular damage and large MCA strokes; and (ii) chronic apraxia of speech and large left MCA strokes. The basis for this limitation of lesion overlap studies is that such studies typically do not evaluate the probability of the deficit in patients with the identified area of lesion, but only the probability of the lesion in patients with the deficit. Thus, it is possible that all patients with apraxia of speech have insular damage, but that few patients with insular damage have apraxia of speech. Such a finding would weaken the hypothesis that planning and programming of speech articulation is an important function of the insula. For this reason, Dronkers (1996) also overlapped the lesions of patients without chronic apraxia of speech. In those patients, lesions were found in parts of the insula, but not in the superior tip of the precentral gyrus, the region found to be affected in the patients who did have the disorder. However, it is possible that some of the patients without apraxia of speech at the

chronic stage did have this deficit earlier. Thus, to evaluate the frequency with which a particular lesion causes a deficit, it is also necessary to evaluate patients at the very onset of stroke, since the deficit may resolve quickly, as other areas of the brain can 'take over' the function of damaged areas soon after stroke (Jenkins and Merzenich, 1987).

Furthermore, deficits may be due to areas of hypoperfusion outside the area of damage visible on CT or conventional MRI scans in acute stroke (Hillis *et al.*, 2003*a*) and chronic stroke (Love *et al.*, 2002). Numerous investigations have demonstrated areas of hypoperfusion beyond the area of infarct that correspond to brain tissue receiving enough blood to survive, but not enough to function normally, using cerebral blood flow studies, including PET and magnetic resonance perfusion imaging (Astrup *et al.*, 1977; Baron *et al.*, 1984; Powers *et al.*, 1985; Warach *et al.*, 1996; Barber *et al.*, 1998; Tong *et al.*, 1998; Beaulieu *et al.*, 1999; Neumann-Haefelin *et al.*, 1999; Heiss *et al.*, 2000; for a review see Baron and Marchal, 2000). Therefore, if there are areas of hypoperfusion that are commonly associated with occlusion/ narrowing of the left MCA (and therefore damage to the insula), such areas of low blood flow might be responsible for the observed apraxia of speech in these cases. Additionally, there may be several areas of the brain that are essential for orchestrating speech articulation, and either damage or hypoperfusion of any one of the areas might lead to apraxia of speech.

In this study, we evaluate the relationship between apraxia of speech and insular damage in acute stroke and test the hypothesis that apraxia of speech is due to hypoperfusion and/ or infarct of Broca's area caused by left MCA narrowing or occlusion (which often, but perhaps independently, causes insular damage). We employ a recently developed methodology, using diffusion-weighted imaging (DWI) and perfusion-weighted imaging (PWI) to identify dysfunctional tissue, and concurrent behavioural testing at onset of stroke to evaluate associations between specific deficits and regions of neural dysfunction before reorganization or recovery. We studied two consecutive series of patients with acute strokes in the territory of the left MCA: one series of 40 patients with insular damage and one series of 40 patients without insular damage (since a single series would be expected to include mostly patients with insular damage, as indicated by previous studies). A battery of speech and language tests was administered to each patient to identify the presence or absence of apraxia of speech, and MRI scans were obtained, both within 24 h of onset of stroke, to minimize the contribution of reorganization after brain injury.

Methods
Subjects
Subjects were adults with first ever, non-lacunar, ischaemic stroke affecting the left MCA territory as determined by MRI. Exclusion criteria were: contraindication for MRI or gadolinium; impaired level of consciousness or muteness; haemorrhage on initial CT or

MRI; intubation; known prior history of uncorrected hearing loss or visual loss, left-handedness, pre-morbid cognitive impairment; or lack of proficiency in English. Patients had a variety of fluent and non-fluent aphasias or no aphasia.

Informed consent was obtained from each subject or from the subject's closest relative (for subjects with impaired comprehension; although these subjects also gave assent for the research), using forms and procedures approved by the Johns Hopkins Medicine Institutional Review Board.

Neuropsychological tests

The test battery included verbal picture description, repetition ($n = 50$ items), oral reading ($n = 50$), and spoken naming of pictures ($n = 60$; 30 nouns and 30 verbs) and objects ($n = 17$). The naming and reading tests included polysyllabic words (e.g. envelope). Normative data for this battery were obtained from 46 hospitalized, asymptomatic control subjects with no evidence of stroke on MRI, who were awaiting surgical repair of unruptured intracerebral aneurysms or awaiting cardiac bypass surgery. Control subjects were comparable in education, age and gender ratio with the patients with stroke. Mean scores for each subtest ranged from 98.0% (SD = 3.1) correct in oral reading to 100% (SD = 0) correct in object naming. Interjudge reliability in scoring performance of patients and control subjects on each of the subtests of this battery was >90% point-to-point percent agreement. A cranial nerve examination, including oral-motor examination, was also done, to evaluate for dysarthria.

Apraxia of speech was defined as: (i) >10% total errors in each oral task (to avoid including those with normal speech, but occasional stumbling on a word); (ii) variable off-target attempts at articulating words; (iii) distorted, groping articulation; and (iv) impaired speech prosody, not attributable to muscle weakness, slowness or reduced range of movement of the muscles controlling speech articulation and phonation (i.e. not due to dysarthria). Apraxia of speech was identified by a speech-language pathologist (K.M.) and by a neurologist (A.H.), without knowledge of imaging results. A random subset of 20 taped transcriptions were re-scored >1 year later by the neurologist and speech-language pathologist independently; there was 100% point-to-point percent agreement on the presence or absence of apraxia of speech using these criteria. Although it may have been better to use standardized tests of apraxia of speech, such tests are rather lengthy for bedside testing in acute stroke. Thus, it should be recognized that our tests may have missed subtle apraxia of speech (in patients with or without insular damage).

Imaging

MRI scans included DWI and fluid attenuated inversion recovery (FLAIR) to identify the extent of damaged or severely ischaemic tissue, and PWI to identify areas of delayed arrival and clearance of a bolus of contrast, which is highly correlated with reduced blood flow (hereafter, 'hypoperfusion'). Scans were done on a GE Signa 1.5 Tesla, echo planar imaging (EPI)-capable system. DWI trace images were obtained using a multislice, isotropic, single shot EPI sequence, with $b_{max} = 1000$ s/mm^2 and repetition time (TR)/echo time (TE) of 10 000/120 ms. Single shot gradient echo EPI PWI, with TR/TE of 2000/60 ms, was obtained with a 20 cm^3 GdDTPA bolus power injected at a rate of 5 cm^3/s; 17 slices provided whole brain coverage.

A neuroradiologist and two technicians, without knowledge of the speech and language test results, identified the presence or absence of abnormality on DWI and/or PWI in five regions of interest on PWI: left insula, posterior inferior frontal gyrus (Broca's area), precentral gyrus, postcentral gyrus and posterior superior temporal lobe (Wernicke's area). Hypoperfused regions were defined as regions in which at least 25% of the region showed >2.5 s delay in time to peak arrival of contrast in that region, relative to the homologous region in the intact hemisphere, since such regions correspond to dysfunctional tissue (Barber *et al.*, 1998; Hillis *et al.*, 2001, 2002, 2003*a*). Subsequently, the same judges evaluated the anterior insula and the superior tip of the precentral gyrus of the insula separately for the presence or absence of dense ischaemia (on DWI) or hypoperfusion (on PWI) defined in the same way. Interjudge reliability in identifying ischaemia and/or hypoperfusion in these regions was 96% point-to-point percent agreement. Association between apraxia of speech and each area of infarct and/or hypoperfusion was identified by χ^2. An area of dysfunction was defined as an area that either had high signal on DWI, indicating dense ischaemia or infarct, and/or was hypoperfused as defined above, since either abnormality causes functional inactivation of the area. Occasionally, regions with high signal on DWI show normal perfusion, since there is sometimes reperfusion of this densely ischaemic tissue in the acute stage that does not restore function.

Results

The mean volume of dense ischaemia or infarction (high signal on DWI, hereafter 'damage') was larger for the cases with insular damage (mean 67.5 ± 65.0 cm^3) than those without insular damage (mean 11.7 ± 23.9 cm^3). Similarly, the mean volume of hypoperfusion (on PWI) was larger for the cases with insular damage (mean 82.5 ± 90.4 cm^3) than those without insular damage (mean 61.3 ± 95.2 cm^3). These results are consistent with the observation of common involvement of the insula in large strokes caused by occlusion of the ICA or MCA.

Analysis of the regions of damage on DWI demonstrated no evidence of an association between apraxia of speech and damage to the left insula [$\chi^2(1) = 0.47$; NS], as shown in Table 1. Apraxia of speech was also independent of DWI abnormality in left anterior insula [$\chi^2(1) = 0.09$; NS], and independent of DWI abnormality in the superior tip of the left precentral gyrus of the insula [$\chi^2(1) = 0.16$; NS], the region previously identified as the most commonly infarcted in patients with chronic apraxia of speech. Figure 1 illustrates cases of damage to this region of the insula without apraxia of speech.

Analysis of the entire region of dysfunctional brain tissue (abnormalities on DWI and/or PWI) also showed no association between apraxia of speech and dysfunction (hypoperfusion and/or infarct) of the left insula [$\chi^2(1) = 2.5$; NS], anterior insula [$\chi^2(1) = 2.8$; NS] or superior tip of the precentral gyrus of the insula [$\chi^2(1) = 0.13$; NS; Table 2]. Instead, the presence of apraxia of speech was associated with hypoperfusion and/or infarct of Broca's area [$\chi^2(1) = 46.4$; $P < 0.00001$; Table 3], but not with other regions evaluated. Results were essentially identical for patients with or without

Table 1 *Relationship between the insular lesion on DWI and apraxia of speech*

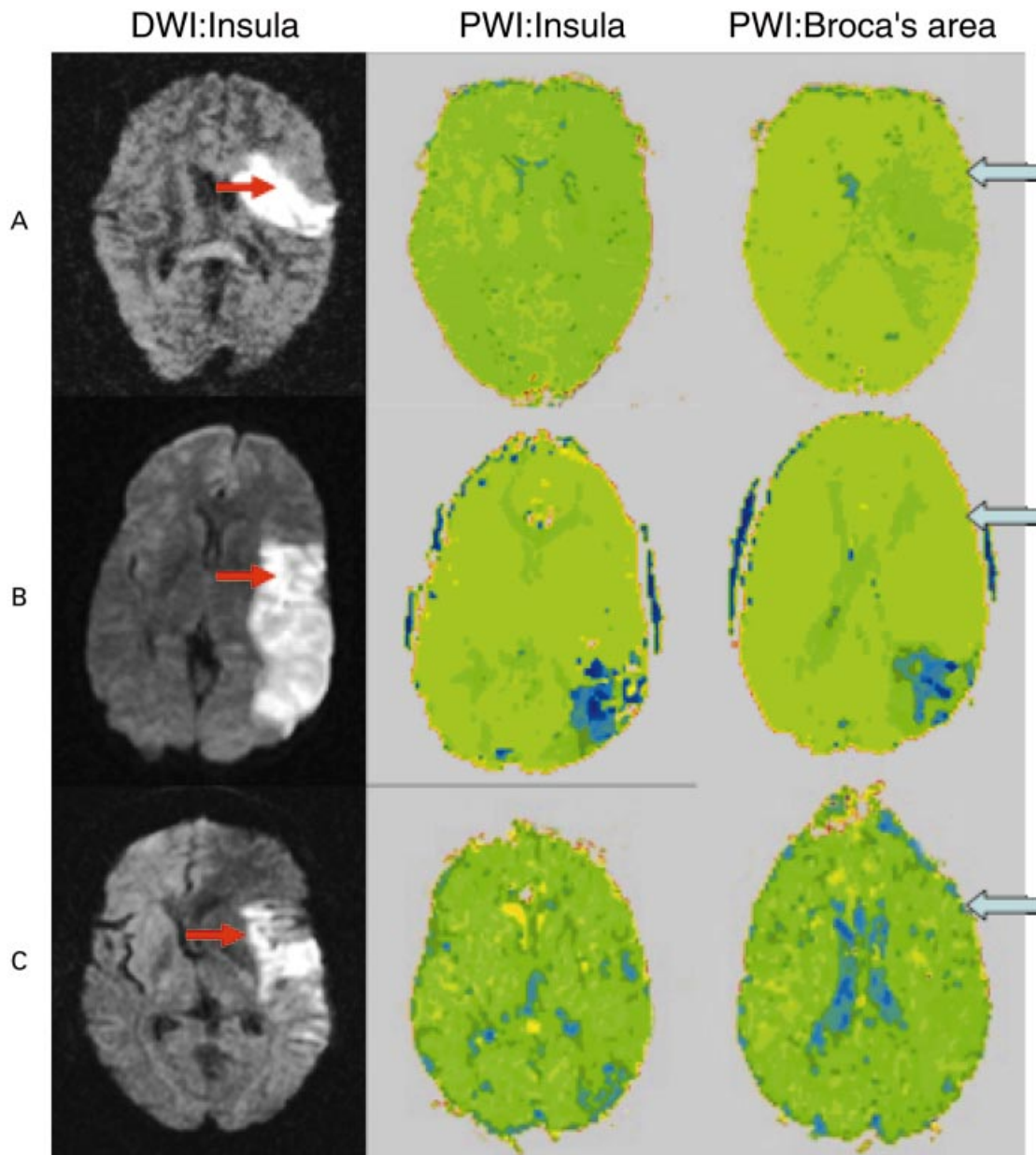|	Left insula damage		Left anterior insula damage	
	Present	Absent	Present	Absent
Apraxia of speech present	14	17	11	20
Apraxia of speech absent	26	23	19	30

Fig. 1 DWI (left scans) and PWI (right and centre scans) of three patients with strokes involving the left superior precentral gyrus of the insula but without abnormality in Broca's area with no apraxia of speech at onset of stroke. (**A**), (**B**) and (**C**) correspond to separate patients. Green areas have normal blood flow; blue areas have delayed time to peak arrival of contrast, corresponding to low blood flow. Red arrows point to the superior precentral gyrus of the insula within the anterior insula. Blue arrows point to Broca's area.

insular damage, providing further evidence that the insular damage was independent of the apraxia of speech, i.e. there was a strong association between apraxia of speech and abnormality in Broca's area in patients with insular damage $[\chi^2(1) = 28.1; P < 0.00001]$ and in patients without insular damage $[\chi^2(1) = 22.4; P < 0.00001]$ (Table 4). Figure 2

Table 2 *Relationship between abnormalities in the left superior precentral gyrus of the insula on imaging and acute apraxia of speech*

	Infarct and/or hypoperfusion of left superior precentral gyrus of the insula	
	Present	Absent
Apraxia of speech present	12	19
Apraxia of speech absent	17	32

Table 3 *Relationship between Broca's area abnormalities on imaging and apraxia of speech*

	Infarct and/or hypoperfusion of left Broca's area	
	Present	Absent
Apraxia of speech present	26	5
Apraxia of speech absent	4	45

illustrates cases of hypoperfusion of left Broca's area and apraxia of speech, with or without insular damage.

Among all 80 patients, there were five patients with apraxia of speech who had neither dense ischaemia (on DWI) nor hypoperfusion (on PWI) in Broca's area (nor in the superior tip of the left precentral gyrus of the insula). All five of these patients had infarct or hypoperfusion of the postcentral gyrus; three also had hypoperfusion or infarct of the precentral gyrus, just posterior to Broca's area. There were also four patients with dense ischaemia or hypoperfusion of Broca's area, but no apraxia of speech by our criteria.

Discussion

This study revealed a strong association between apraxia of speech and dysfunction of Broca's area, demonstrated by DWI and/or PWI. These results contrast with conclusions from a recent, well-designed lesion overlap study and a number of single case studies from which it has been concluded that damage to the left anterior insula (or the superior tip of the left precentral gyrus of the insula within the anterior insula) causes apraxia of speech. Although the lesion overlap methodology is among the most common methods for localizing brain functions, there are two features of this approach that may account for the discrepant findings. First, the area of greatest overlap in strokes is primarily a function of the distribution of blood flow from the cerebral arteries. The insula is one of the most commonly affected regions in all MCA strokes (Caviness *et al.*, 2002), and may be the region of greatest lesion overlap in all strokes caused by MCA

occlusion (Finley *et al.*, 2003). Apraxia of speech, at least in isolation, is typically a transient phenomenon; it persists in patients with large left MCA stroke involving Broca's area and surrounding areas, who at least initially have other symptoms of Broca's aphasia such as agrammatic speech (Mohr *et al.*, 1978). Therefore, chronic apraxia of speech and insular damage may be independent manifestations of large left MCA strokes.

Furthermore, the lesion overlap methodology typically excludes individuals who do not have chronic deficits, some of whom may have damage in the region of interest. Studies of chronically impaired patients often exclude individuals with small stroke; this exclusion occurs because impairments due to small stroke generally resolve in weeks or months, presumably due to reorganization of structure–function relationships (Jenkins and Merzenich, 1987; Chollet *et al.*, 1991; Calautti *et al.*, 2003). Since large MCA strokes characteristically include the insula, strokes that include the insula are over-represented in chronic deficit studies. Unlike many lesion overlap studies, the previous study by Dronkers (1996) did report 19 patients with MCA strokes without insular damage and without apraxia of speech. However, many of these patients (37%) had no speech or language impairment, indicating that they may have recovered from their deficits, which may have initially included apraxia of speech. Our study included all patients with and without insular damage (including large and small stroke), and identified apraxia of speech at onset, before substantial reorganization of structure–function relationships.

Our results do not call into question the association between left anterior insular lesions and chronic apraxia of speech; we expect that the association is highly reliable. However, our results indicate that the observed relationship may not be causative (i.e. may instead reflect the vulnerability of the insula to ischaemia in large MCA strokes). Nevertheless, there is some functional imaging evidence for a possible role of the anterior insula in speech articulation. One PET study showed activation of this region, and not Broca's area, during word repetition, but also during listening (with a conjunction of activations for listening and repetition in the anterior insula; Wise *et al.*, 1999). However, a more recent PET study showed activation in Broca's area, but not the anterior insula, during word repetition and oral reading (Price *et al.* 2003; see also Price *et al.*, 1996). Thus, the role of the anterior insula in planning and executing speech articulation requires further study.

The strong association between apraxia of speech and hypoperfusion/stroke in Broca's area, with or without insular damage, that we observed is more likely to reflect a causative relationship, since we also demonstrated the opposite relationship: a strong association between the absence of apraxia of speech and the absence of abnormality in Broca's area in a series of patients at onset of brain damage. However, Broca's area is unlikely to be the only area essential for orchestrating speech production, since five patients had apraxia of speech with no evidence of functional inactivation

Table 4 *Relationship between Broca's area abnormalities on imaging and apraxia of speech, in cases with and without left insular damage*

	Cases with left insular damage		Cases with normal left insula	
	Infarct and/or hypoperfusion of left Broca's area		Infarct and/or hypoperfusion of left Broca's area	
	Present	Absent	Present	Absent
Apraxia of speech present	13	1	13	4
Apraxia of speech absent	2	24	2	21

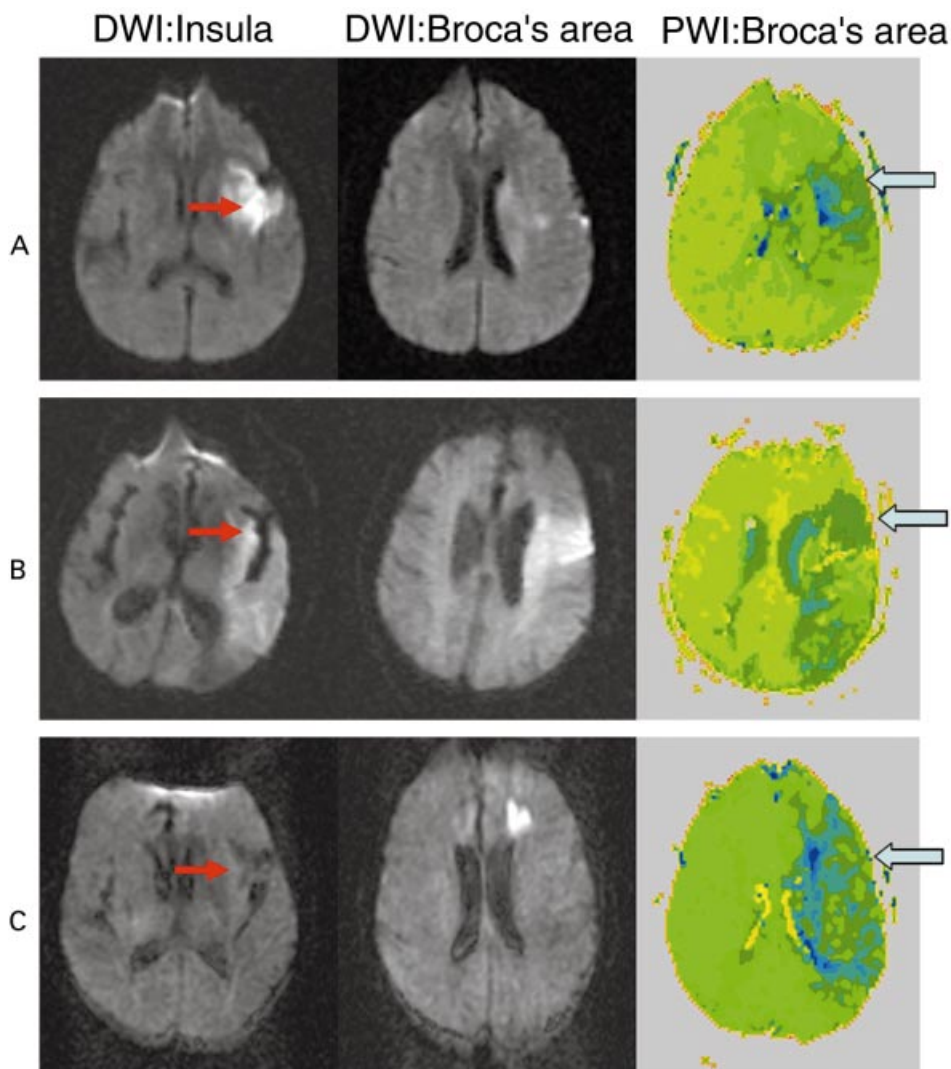**Fig. 2** DWI (left and centre scans) and PWI (right scans) of three patients with apraxia of speech at onset of stroke. (**A**) Stroke involving the left superior precentral gyrus of the insula (left panel), with concurrent hypoperfusion but not stroke in Broca's area (centre and right panel). (**B**) Stroke involving the superior precentral gyrus of the insula (left panel) and Broca's area (centre and right panel). (**C**) Stroke and hypoperfusion in Broca's area (centre and right panel), but not the insula (left panel). Red arrows point to the superior left precentral gyrus of the insula. Blue arrows point to Broca's area.

of Broca's area on MRI. All five of the patients showed abnormalities on DWI and/or PWI in the postcentral gyrus (sensory cortex), along with abnormalities in the precentral gyrus (motor cortex) in three patients. There are at least three potential accounts of these exceptions. First, since speech articulation is a complex process that requires a number of processes such as planning, motor programming, initiation of movement and coordinating the timing and direction of

movements of the speech articulators, it probably depends on a network of brain regions, including parts of Broca's area, the precentral gyrus, the postcentral gyrus (presumably the parts of sensory and motor cortex that represent the face and mouth), and perhaps also the anterior insula. It is possible that each of these regions has some role in execution of speech, such that functional inactivation due to ischaemia in any of these regions might disrupt planning and programming of speech articulation (Square-Storer *et al.*, 1997; van der Merwe, 1997; Square *et al.*, 2001). A second account is that these five exceptional cases did have hypoperfusion and/or infarct of Broca's area, but the individual variability in brain shape, gyral patterns or cytoarchitectural fields (Whitaker and Selnes, 1976; Rademacher *et al.*, 1993; Van Essen *et al.*, 1998) led us to miss the abnormality in Broca's area. A final possibility is that there is individual variability in structure–function relationships, such that Broca's area is critical for orchestrating speech articulation in many but not all individuals.

Similarly, the fact that some previously reported patients with chronic apraxia of speech do not have lesions involving Broca's area (Deutsch, 1984; Kertesz, 1984; Marquardt and Sussman, 1984; McNeil *et al.*, 1990) might be explained by one of the above accounts: the anatomical variability of Broca's area, individual variability in the cortical organization of language, or the possibility of a network of brain regions that function in concert to orchestrate speech articulation. Alternatively, these previously reported patients with apraxia of speech might have had hypoperfusion of Broca's area that was undetectable on CT or conventional MRI.

There were also four patients with hypoperfusion of Broca's area that did not have apraxia of speech. These exceptions might be explained by assuming that Broca's area might have functionally distinct subregions, only some of which are crucial for motor planning and programming of speech (Bookheimer, 2002). Functional inactivation of other subregions would not cause apraxia of speech. An alternative account is that regions showing >2.5 s delay in time to peak arrival of contrast relative to the homologous region of the intact hemisphere (our definition of 'hypoperfusion') might not always correspond to dysfunctional tissue. Previous evidence suggests that hypoperfusion defined in this manner generally leads to dysfunction (Hillis *et al.*, 2001; see also Neumann-Haefelin *et al.*, 1999), but it may not always do so.

We have focused on Broca's area, because this is the only area in which infarct and/or hypoperfusion were significantly associated with apraxia of speech in our study of 80 patients with acute stroke. However, similar arguments can be made regarding the insula, precentral or postcentral gyrus, i.e. that they might be components of a network of brain regions underlying speech articulation.

The results of this study have broader implications for the enterprise of identifying neural correlates of functions on the basis of lesion–deficit associations. More specifically, the results raise questions about conclusions from other studies that have used lesion overlap as the basis for localizing brain functions. In particular, some of the numerous abnormalities associated with insular damage, from sympathetic activation to gait disturbance (Sander and Klingelhofer, 1995; for a review see Cereda *et al.*, 2002), may simply reflect the high frequency of insular damage in large MCA stroke. Results of this study may also account for the wide variety of deficits following strokes restricted to the insula (Cereda *et al.*, 2002). These deficits, which include sensory loss, neuropsychological disturbance, dizziness, falls, dysarthria, non-fluent aphasia and jargon aphasia, may be due to concomitant hypoperfusion of other cortical regions, rather than due to the insular lesion itself. The current study shows that internal carotid artery or MCA stenosis or occlusion frequently leads to both insular damage and hypoperfusion of various regions of the cortex; either can cause clinical deficits. Our results indicate that hypoperfusion (and/or infarct) of left posterior inferior frontal gyrus is strongly associated with acute apraxia of speech, indicating that this region is critically involved in orchestrating speech articulation. Although this finding is not in itself novel, our results illustrate both limitations of traditional lesion overlap studies and an alternative method for identifying neural regions essential for higher cortical functions. Although identifying the area of greatest overlap in lesions among individuals with a particular impairment can be informative (and the method we used in part relies on lesion overlap), it may in part reflect the vulnerability of this region to ischaemia. To avoid the confound of this ischaemic vulnerability, it is necessary to identify the frequency of the lesion causing the deficit, as well as the deficit being associated with the lesion. The former can only be fully evaluated by studying patients at the onset of brain damage (since the deficit may recover quickly).

Studying patients with DWI, PWI and language testing in acute stroke does allow us to study patients, both with and without the deficits and with and without ischaemia in specific brain regions, to identify the probability of the lesion causing the deficit, as well as the probability of the deficit being associated with the lesion. Another advantage of this methodology for identifying areas of brain that are essential for a specific language function is that it permits identification of the effects of small areas of damage or hypoperfusion, before substantial reorganization or recovery. However, there are limitations as well. For example, a lesion may cause deafferentation of a remote area of cortex, causing dysfunction of that region ('diaschisis') without causing hypoperfusion apparent on PWI or bioenergetic failure apparent on DWI. This possibility awaits confirmation by direct comparison of PWI and metabolic functional imaging (e.g. [18F]fluorodeoxyglucose-PET studies), along with detailed cognitive testing to correlate regions of hypoperfusion or hypometabolism with cognitive dysfunction. Another frequently mentioned disadvantage of studying patients in the acute stage of stroke is the variability of performance at this stage; however, we propose that this functional variability in acute stroke can also provide important information about

changes in blood flow in the brain (Croquelois *et al.*, 2003; Hillis *et al.*, 2003*b*).

Acknowledgements

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