The latest on functional imaging studies of aphasic stroke

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Purpose of review

Functional neuro-imaging studies of aphasic stroke offer the potential for a better understanding of the neuronal mechanisms that sustain language recovery. Conclusions, however, have been hampered by a set of unexpected challenges related to experimental design and interpretation. In this review of studies published between January 2004 and February 2005, we discuss imaging studies of speech production and comprehension in patients with aphasia after left hemisphere stroke.

Recent findings

Studies of speech production suggest that recovery depends on slowly evolving activation changes in the left hemisphere. In contrast, right hemisphere activation changes have been interpreted in terms of transcallosal disinhibition that do not reflect recovery because they occur early after stroke, in areas homologous to the lesion, and do not appear to correlate with the level of recovery. There have been few studies of auditory speech comprehension, but unlike speech production, recovery of speech comprehension appears to depend on both left and right temporal lobe activation.

Summary

Together, recent studies provide a deeper appreciation of how the neuronal mechanisms of recovery depend on the task, the lesion site, the time from insult and the distinction between neuronal reorganization that does and does not sustain recovery. Although many more studies of aphasic stroke are required with larger patient numbers and more focal lesion sites, we also argue that clinical diagnosis and treatment requires a better understanding of the normal variability in functional anatomy and the many neuronal pathways that are available to sustain each type of language task.

Keywords

aphasia, degeneracy, functional neuro-imaging, recovery, redundancy

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Abbreviations

fMRI	functional magnetic resonance imaging
PET	positron emission tomography
TMS	transcranial magnetic stimulation

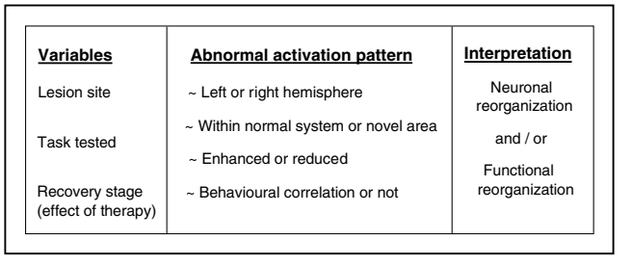
1350-7540

Introduction

Functional neuro-imaging has been used to address a number of different questions that concern how neuronal activation changes after left hemisphere stroke and aphasia. In the past year (2004 to February 2005), these investigations have primarily focused on whether patients compensate for their neurological and functional loss by increasing the level of language-related brain activation in the left or the right hemisphere. A second question relates to whether activation changes occur within the normal set of language regions, or in 'novel' areas that are not normally activated during language processing. Other questions relate to the time course of activation changes and how activation changes correlate with behavioural recovery (see Fig. 1).

Recent interpretations of functional imaging data from aphasic patients have led to a much clearer distinction between neuronal reorganization that does and does not sustain language recovery. For example, increased activation related to transcallosal disinhibition does not necessarily relate to recovery, whereas increased activation related to compensatory strategies may be critical for a functional recovery. As discussed below, a variety of evidence suggests that many of the right hemisphere activation changes after aphasic stroke are a consequence of transcallosal disinhibition rather than reflecting compensatory changes in speech processing. Finally, the conclusions drawn appear to depend critically on the language task investigated and the anatomical location and extent of the lesion. The literature review on recent (2004 to February 2005) functional magnetic resonance imaging (fMRI), positron emission tomography (PET) and magnetoencephalography studies of aphasic stroke that follows is therefore sectioned according to whether the authors investigated speech production or auditory speech comprehension. See Table 1 for a list of studies [1•,2••,3•–5•,6••,7•,8•]. We then discuss future directions and questions that we hope will lead to further advances in our understanding of recovery from aphasia.

Figure 1. Current functional imaging approaches to aphasic stroke



The typical variables, effects and interpretations reported in recent studies.

Speech production tasks

Five fMRI studies of speech production after aphasic stroke [1•,2••,3•–5•] have recently been published. Naeser *et al.* [1•] reported activation during propositional speech (describe a picture) in four patients with non-fluent aphasia (hesitant, agrammatic speech) after large, left middle cerebral artery infarction. Increased activation was observed in patients compared with control subjects in the right supplementary motor area and right sensorimotor cortex during speech but not during non-speech. This indicates right hemisphere changes after left hemisphere damage. However, irrespective of whether the patients were speaking or not, activation in all the right hemisphere regions of interest was higher in patients than in controls. This overactivation in right hemisphere language homologues was therefore interpreted as part of the cause of the patients' hesitant poorly articulated speech, rather than reflecting compensatory activation. A similar conclusion can be drawn from the studies by Fernandez *et al.* [2••], Abo *et al.* [4•] and Xu *et al.* [3•].

Fernandez *et al.* [2••] reported activation for rhyme decisions (does the name of a picture rhyme with a heard word) in a patient with a large left temporoparietal lesion at two different timepoints in recovery (one month and one year after stroke). Irrespective of the recovery stage, the patient showed increased right temporoparietal activation compared with 10 control subjects. Left hemisphere changes were only observed a year after stroke when performance had improved. This suggests that left rather than right hemisphere changes were important for long-term recovery. Moreover, the right hemisphere activation was in the homologue of the damaged left temporoparietal region. It may therefore reflect an early loss of transcallosal inhibition, as proposed previously by Rosen *et al.* [9] and Blank *et al.* [10], who observed increased right frontal activation after left frontal damage, but no correlation of right frontal activation with the recovery level (see Fig. 2) [11].

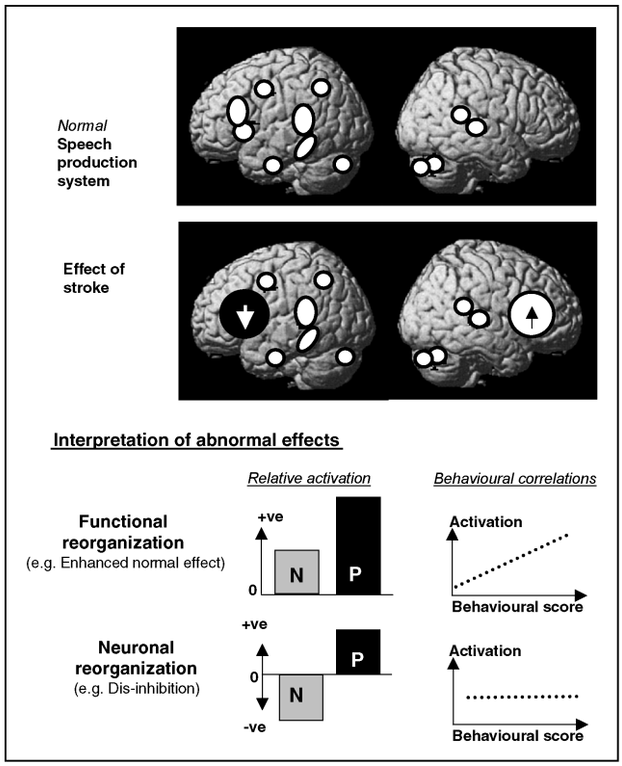
Abo *et al.* [4•] illustrated how right hemisphere activation depends on the lesion site. They observed right frontal

Table 1. Functional imaging studies of aphasia published from January 2004 to February 2005

Authors	Patients	Controls	Time tested (post stroke)	Modality	Imaging tasks/stimuli
Speech production tasks					
Naeser *et al.* [1•]	4	4	4–9 years	fMRI	(1) Overt propositional speech (2) Rest (checkerboard)
Fernandez *et al.* [2••]	1	10	T1: 1 month T2: 1 year	fMRI	(1) Word picture rhyming (phonological) (2) Word picture semantic matching task (3) Visual stimulus (baseline)
Xu *et al.* [3•]	3	6	10–35 days	fMRI	(1) Covert generation of a word semantically related to a visually presented word (2) Fixation point
Abo *et al.* [4•]	2	6	60 months	fMRI	(1) Word repetition (2) Rest
Peck *et al.* [5•]	3	3	T1: $>$ 6 months T2: After 8 weeks treatment	fMRI	(1) Overtly generate a single exemplar in response to a category name (2) Rest quietly
Speech comprehension tasks					
Sharp *et al.* [6••]	9	18	14–145 months	PET	(1) Semantic decision task (2) Syllable decision task (Controls heard stimuli in both clear speech and noise-vocoded speech)
Zahn *et al.* [7•]	7	14	$\geq$ 6 months	fMRI	(1) Phonetic (reversed words discriminated from signal correlated complex sounds) (2) Lexical (auditory lexical decision task) (3) Semantic (superordinate category decision between animal and other natural names)
Breier *et al.* [8•]	6	6	$\geq$ 10 months	MEG	(1) Auditory word recognition (2) Fixation
Fernandez *et al.* [2••]	See above				

fMRI, functional magnetic resonance imaging; MEG, magnetoencephalography; PET, positron emission tomography.

Figure 2. Neuronal versus functional reorganization



Top row: An illustration of the left and right brain areas activated during normal speech production compared with rest (data from Warburton *et al.* [11]). Second row: a hypothetical illustration of the effect of left inferior frontal damage (black circle with arrow indicating decreased activation compared with normal subjects) on right inferior frontal activation (white circle with arrow indicating increased activation compared with normal subjects). Interpretation of the right hemisphere effect (below) depends on determining whether activation in this area relative to baseline (positive = above baseline, negative = below baseline) is 'inhibited' (i.e. below baseline) in neurologically normal (N) control subjects; and whether activation over a population of patients (P) depends on their level of recovery as measured by their behavioural score.

activation during auditory repetition in a patient with left frontal damage, but not in control subjects or a patient with left temporoparietal damage. Conversely, their patient with left temporoparietal damage showed right inferior parietal activation that was not observed in control subjects or the patient with the left frontal lesion. Likewise, Xu *et al.* [3•] observed right inferior frontal activation during covert word generation in a patient with left frontal damage but not in two patients with left temporoparietal damage. This suggests that, at least for speech production tasks, the site of right hemisphere activation depends on the site of the lesion. With respect to the contribution of this right hemisphere activation to recovery, both patients reported by Abo *et al.* [4•] had made a full recovery from initial aphasia. Therefore, it was not possible to interpret the right hemisphere activation. However, the results of Xu *et al.* [3•] suggest that right frontal activation does not relate to recovery because their patients participated in the brain imaging study within a month of their stroke before they had recovered their speech. The study by Xu *et al.* [3•] therefore provides more evidence [2••,12] that right hemisphere activation changes occur rapidly after cerebral infarction and do not reflect the level of recovery. Overall the effect of the lesion site, the timing of onset and the independence from recovery status are all consistent with an explanation of right hemisphere activation in terms of transcallosal disinhibition rather than compensatory mechanisms.

A complementary but slightly more complex perspective is offered by Peck *et al.* [5•]. The authors reported activation for verbal fluency (generate words that are examples of given categories compared with rest/wait for next stimulus) in three aphasic patients with large left hemisphere lesions and three neurologically normal controls. All subjects activated selected regions of interest in the right hemisphere, but the time taken for the haemodynamic response to reach its peak was longer in the patients than control subjects. Critically, after rehabilitation the timing of right hemisphere responses returned towards normal. This suggests that recovery involved re-establishing 'normal right hemisphere responses'. Unfortunately, there were insufficient participants in the study by Peck *et al.* [5•] to ascertain whether right hemisphere activation was initially more activated in the patients than the controls subjects. If right hemisphere activation was initially higher, as well as slower than normal, but returned to normal levels after recovery was complete, this would be consistent with recovery re-establishing right hemisphere inhibition. If, on the other hand, the distinction between the patients and controls was only in the timing of responses, then the findings reported by Peck *et al.* [5•] are not entirely consistent with those reported by Naeser *et al.* [1•] and Fernandez *et al.* [2••] above.

In summary, all the recent functional imaging studies of speech production after aphasic stroke suggest neurofunctional changes in the right frontal or temporal regions. Right frontal activation is more likely to be observed after left frontal damage [3–5•,9,10], whereas right temporoparietal activation is more likely to be observed after left temporoparietal damage [2••,4•]. Right hemisphere changes do not, however, appear to reflect the level of recovery [2••,3•,4•,9,10,12], although see Peck *et al.* [5•]. They may therefore reflect transcallosal inhibition (maladaptive neuronal reorganization) rather than functional compensation (see Fig. 2).

Auditory speech comprehension tasks

Four studies of auditory speech comprehension after aphasic stroke have recently been published, which used fMRI [2••,7•], PET [6••] or magnetoencephalography

[8•]. One of the difficulties that may be limiting the number of such studies is that speech comprehension is difficult to assess without an overt response (manual or vocal). The four studies discussed in this section therefore resorted to tasks that required a manual motor response to indicate that the meaning of the words had been accessed. In particular, subjects were asked to decide whether or not the meaning of a heard word referred to an animal name [7•], or the same semantic category as a simultaneously presented picture of an object [2••]. In the PET study by Sharp *et al.* [6••], subjects heard three different words and had to decide whether the meaning of the first (e.g. 'beach') was more related to that of either the second (e.g. 'island') or third (e.g. 'mountain'), and in the magnetoencephalography study by Breier *et al.* [8•], subjects were asked to lift their left index finger whenever they detected a word that they had heard before the experiment (i.e. a recognition memory task).

The speech comprehension study by Fernandez *et al.* [2••] was conducted on the same patient as their study of speech production discussed in the previous section and at the same timepoints (one month or one year after stroke). Similar results were revealed for speech comprehension as reported above for speech production. In other words, compared with the normal control group, there was increased right temporoparietal activation in the first month after a left temporoparietal lesion, and this was preserved and followed one year later by increased left middle temporal activation. Notably, however, unlike the speech production task, the patient was able to perform the speech comprehension task normally at both testing sessions. Therefore, there is no clear link between either the left or right hemisphere activation changes with recovery processes.

Breier *et al.* [8•] also emphasized the role of left hemisphere perilesional activation in speech comprehension recovery. Using magnetoencephalography, they found that their six chronic aphasic patients had reduced activation, compared with six control subjects, in the left superior temporal gyrus with increased left hemisphere activation outside the superior temporal gyrus. Yet again, no significant relationship was observed between speech comprehension and right hemisphere activation. Sharp *et al.* [6••] painted a different picture. They investigated nine patients with left superior temporal lobe lesions, and observed a direct correlation between right anterior fusiform activation and good performance during their complex auditory semantic association task. This suggests that right inferior temporal lobe activation does play a critical role in speech comprehension tasks. Critically, however, the correlation in right temporal activation and behaviour was also observed in neurologically normal subjects when they heard degraded speech. Sharp *et al.* [6••] were therefore able to demonstrate that, although right temporal lobe activation in the patients did contribute to good performance, it did not reflect the recruitment of novel areas that were not engaged by neurologically normal controls. A similar conclusion was reached by Zahn *et al.* [7•], who analysed fMRI data from individual subjects, and noted that semantic activation in seven patients with large left hemisphere lesions was primarily observed in the left and right hemisphere areas that were also activated in all, or a subset, of the neurologically normal controls.

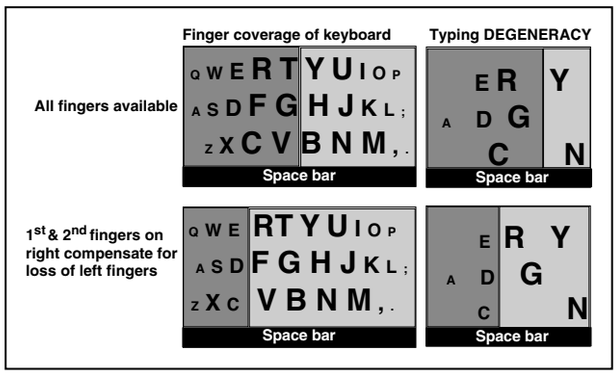
Future directions

Here we argue that an understanding of how language recovers after stroke requires an understanding of structure–function relationships that are established in the neurologically normal brain before injury. This is because extrinsic connections do not form 'de novo' in the mature brain. On the contrary, functional reorganization involves learning (or experience)-dependent plasticity that is mediated by changes in the function or number of synapses (i.e. synaptic plasticity) within pre-existing systems. The neuronal mechanisms that underlie recovery will therefore be present in the neurologically normal brain, and studies of structure–function mappings in neurologically normal subjects can be used to guide and interpret findings from neurologically damaged individuals.

The observation that language can recover after aphasic stroke suggests that there must be more than one set of brain structures that can sustain a given language task. In other words, there is 'degeneracy', defined as the ability of structurally different elements to perform the same task [13–16]. The term 'degeneracy' is often conflated with redundancy [7•,17], but this is not correct. Redundancy is the inefficient use of degenerate structures [18]. For example, if two structures can perform the same function, it is redundant to use both structures at the same time, or a latent structure only when the prepotent structure is not available. Degeneracy does not have to entail redundancy, it can be the converse, which is efficient. For example, degenerate structures are efficient if each structure also has multiple functions. Consequently, efficient degenerate systems have many to many, structure–function relationships (see Fig. 3).

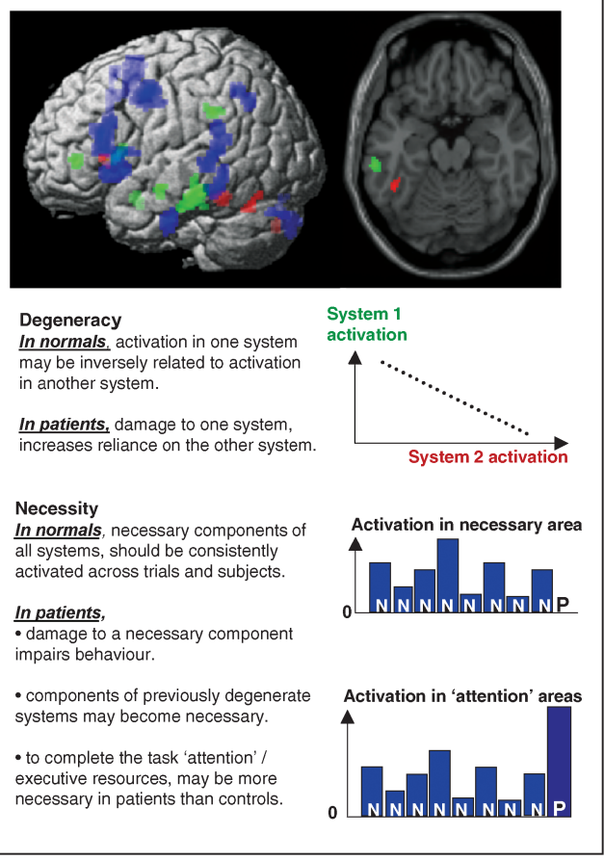
How might we dissociate the many to many, structure–function mappings that underlie recovery? One approach is to explore individual variability in normal and abnormal activation patterns. If different individuals engage different systems, then activation in one system may be inversely related to activation in another (see Fig. 4). Normal variability can therefore provide strong hypotheses for the components of different systems, but a full appreciation of degeneracy requires the integration of both normal and patient data [14,19]. In particular,

Figure 3. Degeneracy versus redundancy: touch-typing analogy



Degeneracy and redundancy are illustrated with an analogy to the structure–function relationships required for touch typing. The size of the letters indicates the position of the fingers (largest letters for first finger, smallest letters for fourth finger) typically used in touch typing. When all fingers are available, typing is fastest when the left-sided letters (in dark grey) are touched by the left fingers, the right side letters (in light grey) are touched by the right fingers, and the space bar (in black) is touched by one of the thumbs. The right hand column indicates the fingers used to type 'DEGENERACY'. Loss of the first and second fingers on the left hand would require functional reorganization from the first and second fingers on the right hand or the third and fourth fingers on the left hand. Recovery for finger loss therefore occurs in the context of degenerate many to many structure–function relationships that are efficient, not redundant. In contrast, there are two thumbs for the same function (press space bar) and the thumbs have no other function. This degenerate structure–function relationship is therefore redundant (in the context of touch typing).

Figure 4. Degeneracy versus necessity



Top row: An illustration of the left hemisphere activation during normal speech production in two subjects A and B (data from Warburton *et al.* [11]). BLUE: increased activation common to subjects A and B; RED: increased in subject A but decreased in subject B; GREEN: increased in subject B and decreased in subject A. Threshold $P < 0.001$ uncorrected for all effects. Degeneracy: Activation in either red OR green areas is sufficient to facilitate task performance (e.g. by different strategies). Subjects either use one system or the other. Therefore as activation goes up in one system it goes down in the other. Necessity: If an area is a necessary component of all possible systems, then it should be activated in all trials; and if damaged, there will be a task performance deficit. Some areas may be necessary in patients but not normal individuals, if alternative (degenerate) systems are damaged in the patients.

patient studies increase individual variability in the activation pattern by increasing reliance on intact systems and decreasing activation in undamaged components of systems that include the damaged area(s). In other words, areas in which activation is reduced compared with normal individuals are likely to be part of the same system as the damaged areas. Conversely, areas where activation is increased are likely to be part of a different system to those where activation is reduced.

Finally, we note the potential contribution of transcranial magnetic stimulation (TMS) studies for interpreting functional imaging data from aphasic stroke patients. Two recent studies have used TMS to determine whether enhanced right hemisphere activation after neurological damage contributes to recovered speech production. If TMS impairs speech production, a positive contribution is indicated [20]. Conversely, if speech production improves, TMS may be suppressing irrelevant or interfering activation, e.g. maladaptive disinhibition [21]. Martin *et al.* [21] have even suggested that TMS may provide a novel, complementary treatment for aphasia.

Conclusion

It is estimated that functional neuroimaging is currently used by several thousands of investigators worldwide, but our search for functional imaging studies of speech production and auditory speech comprehension within the past year only revealed eight publications with data from a total of 35 aphasic stroke patients. The paucity of aphasia data may relate to the time-consuming nature of the investigations, the constraints on patient selection, and the difficulties in interpreting activation changes in the context of limited behaviour [19]. Future progress obviously requires a far greater commitment to functional imaging studies of aphasic stroke patients, so that the effect of the lesion site, task and therapy can be better understood. In addition, however, we also need a better understanding of structure–function relationships in the neurologically normal brain.

We conclude that functional neuroimaging studies of aphasia are still in their infancy. They may eventually facilitate clinical diagnosis and treatment, but only when we have a better understanding of the degenerate neuronal pathways that are available to sustain each type of speech task.

Acknowledgements

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

- • of special interest
- •• of outstanding interest

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This fMRI study shows overactivation in right hemisphere regions of interest that were not all specific to speech production. The authors conclude that right hemisphere activation is maladaptive rather than compensatory.

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This fMRI study shows how abnormal activation during speech comprehension and production changes over the course of recovery. In particular, enhanced right hemisphere activation was observed early and persisted, whereas enhanced left hemisphere activation was only observed after recovery.

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This study shows abnormal inferior frontal activation during severely impaired speech production 10 days after a left frontal stroke. The right frontal activation appeared to be specific to the lesion site because it was not observed when the lesion involved the temporal lobes.

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This fMRI study shows that the site of right hemisphere speech-related activation after aphasic stroke depends on the site of the lesion: Right frontal activation followed left frontal damage and right temporoparietal activation followed left temporal damage.

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This fMRI study demonstrates that abnormal activation after aphasia can be characterized in terms of the time taken for activation to reach a peak.

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This PET study of auditory semantic processing shows that left superior temporal lesions reduce activation relative to control subjects in the left fusiform, and that good performance is correlated with right fusiform activation. Contrary to other studies, this study shows the importance of right hemisphere activation and that abnormal effects in patients can be induced in neurologically normal subjects by distorting speech perception.

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