Language systems in normal and aphasic human subjects: functional imaging studies and inferences from animal studies

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The old neurological model of language, based on the writings of Broca, Wernicke and Lichtheim in the 19th century, is now undergoing major modifications. Observations on the anatomy and physiology of auditory processing in non-human primates are giving strong indicators as to how speech perception is organised in the human brain. In the light of this knowledge, functional activation studies with positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) are achieving a new level of precision in the investigation of language organisation in the human brain, in a manner not possible with observations on patients with aphasic stroke. Although the use of functional imaging to inform methods of improving aphasia rehabilitation remains underdeveloped, there are strong indicators that this methodology will provide the means to research a very imperfectly developed area of therapy.

The study of language keeps philosophers, semioticians, phoneticists, linguists, neurolinguists, aphasiologists, psychologists, neuropsychologists, and the occasional neurologist happily occupied throughout their working life-time. Some of this academic interest has been fuelled by the study of impaired communication after stroke or head injury. The patient may live for years after the original brain injury and, if the aphasia persists and is considered to be of theoretical interest, academics will continue to test hypotheses by experimenting on impaired speech comprehension and/or production. From the patient's perspective, aphasia isolates professionally and socially: the human dependence on the spoken word explains why deafness isolates more than blindness. Unfortunately, progress in research on the functional architecture of language has not been matched by similar advances in the rehabilitation of aphasia.

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Functional neuroimaging, with positron emission tomography (PET) and, more recently, functional magnetic resonance imaging (fMRI), was introduced in 1988[1] as the new tool to study language and other brain functions. It is sometimes overlooked that the use of a change in regional cerebral blood flow (rCBF) to index local neural activity in response to

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language tasks had been in use over the previous three decades[2]: but it was the combination of tomographic scanning (with equal sensitivity throughout the brain), short-lived radiotracers to measure blood flow (with half-lives and radiation dosimetry that permitted repeated measures on a subject during one scanning session) and the introduction of sophisticated data analysis software that resulted in an explosion of interest in the technique. Although there has been a shift from PET to fMRI over the last decade, each technique has its advantages for the study of language. fMRI combines greater spatial resolution, faster temporal resolution and no exposure of the subject to radiation. Perhaps its major advantage is to study haemodynamic changes after perception or response to a single stimulus (event-related imaging), allowing true experimental randomisation. The blocked designs necessary in PET, as one CBF measurement is performed over 1–2 min, cannot distinguish between transient responses to repeated stimuli, which are summed over the scanning period, or a steady-state change (set shift) in readiness for the repeated stimuli and the responses to them. Furthermore, it may be an advantage to bin scan data after correct and incorrect responses to stimuli separately, as the haemodynamic responses to 'hits' and 'misses' may be quite different[3]. However, PET has four advantages for the study of language: (i) it does not lose sensitivity and spatial localisation in important anterior and medial temporal lobe structures, a (current) problem with fMRI due to susceptibility artefacts and geometric shifts[4,5]; (ii) its lower spatial resolution makes it orders of magnitude less susceptible to movement artefacts time-locked to stimulus and response, as occurs with overt articulation (most fMRI studies of word retrieval use covert responses); (iii) it does not create the din that is a feature of data acquisition in an MR scanner, requiring special techniques when important acoustic features in auditory stimuli may be masked[6]; and (iv) in the serial study of aphasic patients, it is the author's anecdotal experience that patients are far more likely to agree to come back for a second PET scan than to go back into a MRI magnet, a much more intimidating environment. It is also worth noting that the greater spatial resolution of fMRI is of less advantage in cognitive studies than may be suggested by its enthusiasts. Results in single subjects, closely matched to their individual anatomy, works well when investigating primary sensory and motor cortex and early sensory association or premotor cortex: the signal is stronger and more reliable across subjects. In other cortical regions, the signal-to-noise ratio is less advantageous and the ability to detect signal within individual studies is less reliable. Thus, group studies on cognitive, including language, processing are the norm. Each subject's brain within a study group has to be anatomically normalized into the same stereotactic space. To allow for individual variations of gyral and sulcal anatomy, the image data have to be

smoothed. Although the peaks of activity in higher resolution image data are always resolved better than in lower resolution data, it is apparent to the eye that the smoothed fMRI images in grouped language studies may be little different from the grouped images generated by modern PET cameras[7]. Nevertheless, a recent study of voice perception using fMRI convincingly demonstrated activation confined to the dorsal bank of each superior temporal sulcus[8], without spread into the ventral bank, a confidence in localisation that cannot be achieved even with modern PET cameras.

Clinical studies have been of major importance in identifying the functional architecture of speech processing: observations on double dissociations between patients have identified a modular structure to the language system[9]. Indeed, functional neuroimaging studies have depended heavily on this knowledge for study design and data interpretation. However, the neuropsychological technique of lesion-deficit analysis has proved to be an uncertain method of defining the location of the neural sub-systems involved in language processing. Until recently, lesion localisation was made by post mortem examination. The ability to obtain such information from a clinically interesting patient meant seizing the opportunity after a whim of nature, an unreliable method but one that ensured the enduring fame of Broca and Wernicke. However, the excellent anatomical information that was obtained in a few cases was often confounded by the inadequacy of the behavioural testing in life. The reverse was also true: detailed behavioural testing on interesting patients was not supported by anatomical information, and the site of the lesion was inferred from the aphasic syndrome of the patient. Thus, if the patient's profile on a standardised test battery fitted best with the syndrome of Broca's aphasia, it was assumed that the lesion included the posterior left inferior frontal gyrus, even though lesion localisation inferred from an aphasic syndrome is unreliable[10]. The introduction of X-ray CT scanning and then structural MRI allowed more precise lesion localisation at the time of patient testing, but without a major advance in our understanding of the cortical organisation of language at the systems level. This is because of the problem of lesion distribution. Ablation studies in non-human animals are placed with great care, and often post mortem examinations are performed after the behavioural experiments to confirm the boundaries of the lesion. The unsubtle lesions occurring as the consequence of cerebrovascular disease, necrotising viral infections, *etc*. may destroy cortex, local white matter connections, major white matter tracts connecting remote cortical regions, sub-cortical nuclei, and their reciprocal connections with cortical areas. No lesion experiment in a non-human animal, relating structure to function, would be accepted for publication if clipping of a major arterial branch produced the focal injury. For obvious reasons, human studies have depended on nature's experiments, and

much more liberal scientific standards have applied. As a result, syndromes have been described that may be associated with lesions at various locations. This has sometimes been attributed to marked inter-subject differences in the cortical organisation of function, which, if true, would mean that studies of structure–function relationships in the human, other than early perceptual and motor processes, are meaningless. It would seem much more plausible that broadly similar clinical syndromes may result from very differently sited cortical, sub-cortical or tract lesions within distributed neural systems that are essentially similar between subjects with the same handedness and uneventful development.

The value that functional neuroimaging brings to language research is to improve the perspective on the distributed anatomy of language. Thus, it can be used in normal subjects to identify where modular language processors are located with considerable precision. It has been argued that the traditional Broca's area in the left inferior frontal gyrus can be sub-divided into three regions: one that is posterior and superior and is involved in the sound structure (phonology) of language; a second, anterior and ventral that is concerned with the meaning of words (semantics); and a third, lying in-between the first two regions, that is involved in meaning conveyed by sentence structure (syntax)[11]. Of particular clinical relevance is the ability to determine shifts of function after focal brain lesions, and how these may be potentially modified or even induced by behavioural or drug therapy.

Communication: of mice, birds, monkeys and man

Speech is the most complex motor act we perform. It involves control of breathing, vocal cord tension and the position of the articulators (soft palate, tongue, lips and jaw) with adjustments over a few tens of milliseconds. It was the descent of the larynx during human evolution that allows us the remarkable range of movements of the tongue required to achieve the production of a wide range of speech sounds[12]; although any one language makes use of only a small number of the 800 possible speech sounds (phonemes) that can be produced by the human vocal tract. Speech sounds contain complex spectral and temporal information. At any one point in time, three or four frequencies carry the greatest energy, these so-called formants being the result of resonances created by filtering the laryngeal sound source by positioning of the articulators. As the articulators change position there are changes in the frequencies of the formants, occurring over tens to hundreds of milliseconds (Fig. 1). Although these transients are clearly important cues in speech perception, despite much effort it has never proved

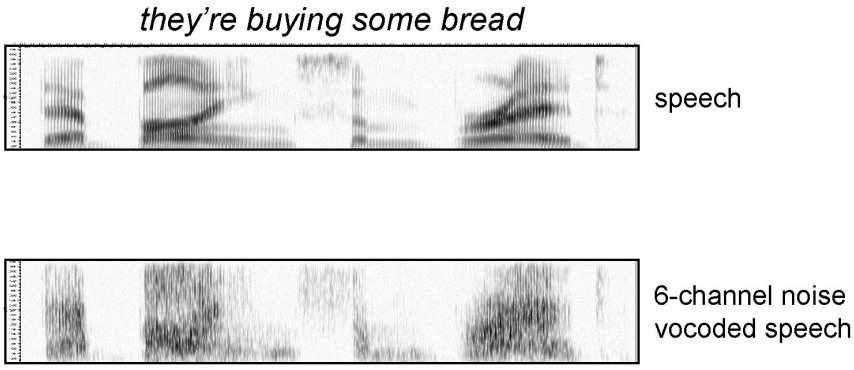

Fig. 1 Speech spectrograms of normal speech (top panel) and the same phrase as 6-channel noise-vocoded speech. Frequency is along the y-axis and time is along the x-axis. The amplitude at a particular frequency and time is represented by the intensity of shading.

possible to identify one acoustic feature that makes speech intelligible[13]. It is evident from Figure 1 that there is considerable redundancy in the spectrotemporal information carried by the speech signal. Dividing the frequency range of speech into 6 broad bands and filling each band with white noise when there is sound within that spectral range in the original speech signal results in a spectrogram showing considerably degraded spectral and temporal information compared to the original. Despite this, with little training a native speaker of the language finds this noise-vocoded speech intelligible[14], although other features carried in the speech signal, such as the identity, age and sex of the speaker, are lost. Outside the acoustic laboratory, a listener at a cocktail party can still make a fair attempt at politely coping with the utterances of a speaker with an unfamiliar dialect, talking with a hot *vol-au-vent* in his mouth, while the babble of competing speech continues all around; revealing a talent for not only correctly categorising severely distorted speech as individual intelligible words, but also in streaming irrelevant speech sounds coincident with the attended speech.

A vocal apparatus capable of generating speech and an acoustic system that can analyse speech sounds underlies the evolution of language. However, parrots can speak and mice can discriminate between complex sounds in much the same way that humans perceive speech[15] – yet neither species possesses language. Leaving aside the important 'grooming' aspect of communication (such as an interchange, 'warm for the time of year'; 'yes, but it might rain later'), language exists primarily to place information from the mind of the speaker into the mind of the listener. Thus, the speaker and listener must share a common language that maps on to a common core of knowledge. This definition of language is based on conceptual ('denotative' or 'cognitive') meaning[16]. Communication is

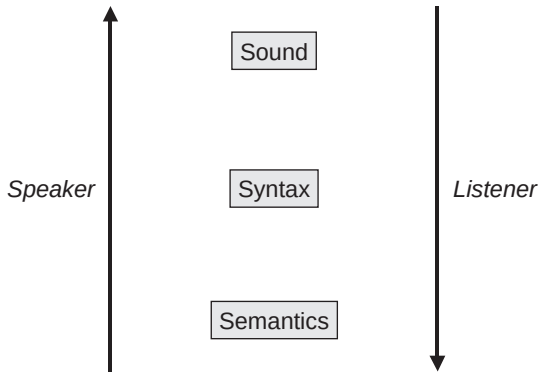

Fig. 2 Simple information processing model for speech production (speaker), reversed for speech perception (listener).

rendered unambiguous by the selection and ordering of words by the speaker. In essence, the transaction between speaker and listener can be represented as a simple information processing model (Fig. 2). Within this broad overview, there is considerable, and potentially very important, detail in each of the three levels specified. These systems operate automatically, and to separate out these levels on the basis of a difference in regional blood flow between one behavioural condition and another may not be easy (or even possible). Furthermore, much of what is communicated has meaning that is other than conceptual. For example, there may be an emotional response to what is said, and the neural instantiation of affective meaning may be different from that associated with conceptual meaning. At the highest level, comprehending within the context of who is speaking about what, *i.e.* having a 'theory' about the underlying mental workings of the speaker and interpreting his/her utterances in the light of this 'theory', is critical for effective communication. This skill is lacking in autism, and studies with functional neuroimaging have led to the hypothesis that there is a 'module' for theory of mind in the medial frontal lobes, in paracingulate cortex[17].

Notwithstanding these complexities, the rest of this section will attempt to address: (i) where perceived speech is processed in auditory cortex; (ii) where the output of this auditory processing goes to map the verbal sound to meaning; and (iii) which brain regions are involved in formulating, constructing and articulating an utterance.

The auditory perception of speech

Broadly speaking, there are two extreme positions on this topic. One is that we have evolved to segregate speech sounds at the very earliest level

of cortical auditory processing and, in addition, speech perception and production are intimately linked so that motor knowledge of articulatory gestures influences the acoustic analysis of speech sounds[18]. The other is that speech sounds are processed like any other environmental sound up to the point where the encoded complex phonetic cues and features map on to language processors. The latter hypothesis considers speech perception and production to be independent. These debates are unresolved, and each hypothesis might be associated with quite different results when performing functional neuroimaging studies of speech, depending on study design. A reasonable compromise position may be to consider that speech is unlikely to be segregated as early as primary auditory and early association cortex. However, humans, in common with song birds, have to learn their repertoire of utterances after birth (or hatching). This requires a strong interplay between sound production and perception, the acoustic template being the sounds produced by accomplished speakers (or songsters) in the immediate environment[19]. Using this template, the infant (or hatchling) self-monitors and self-corrects its own attempts to mimic these sounds. This system becomes 'hard-wired' early in life, so that accents and dialects become quickly established: we usually speak with ze foreign accent in a language we have acquired after the age of 5 years. Therefore, speech perception and production are intimately linked from birth, and this functional link is likely to persist into adulthood. Indeed, there is evidence that speech perception modulates the excitability of the motor innervation of the tongue[20]. A recent hypothesis about language acquisition has incorporated the discovery of 'mirror neurons' in a plausible equivalent of Broca's area in the monkey brain. These neurons respond to manipulative gestures by other monkeys and encode for similar manipulations by the observer, which has led to speculations that human articulatory gestures may be similarly acquired by infants observing articulatory gestures by competent speakers[21,22]. However, this is unlikely to be a major influence as, except for jaw and lip movements, the motor act of articulation is hidden from the view of an observer. Furthermore, congenitally deaf children never learn to articulate well but congenitally blind children do. The 'mirror neuron' hypothesis of language acquisition becomes more plausible once it is realised that sounds as well as light can be 'mirrored'. There is no reason why frontal neurons should not respond to sounds that result from articulatory manipulations, whether they can be visually observed (lip movements) or not (tongue movements)[23]. Potential support for such a hypothesis comes from the finding that there are inferior frontal neurons that respond to auditory stimuli, simple or complex[24].

Non-human primates have an auditory cortex capable of discriminating between complex environmental sounds, including the various vocalisations of their own species. Although it is often argued that there is no animal model of language, and hence language can only

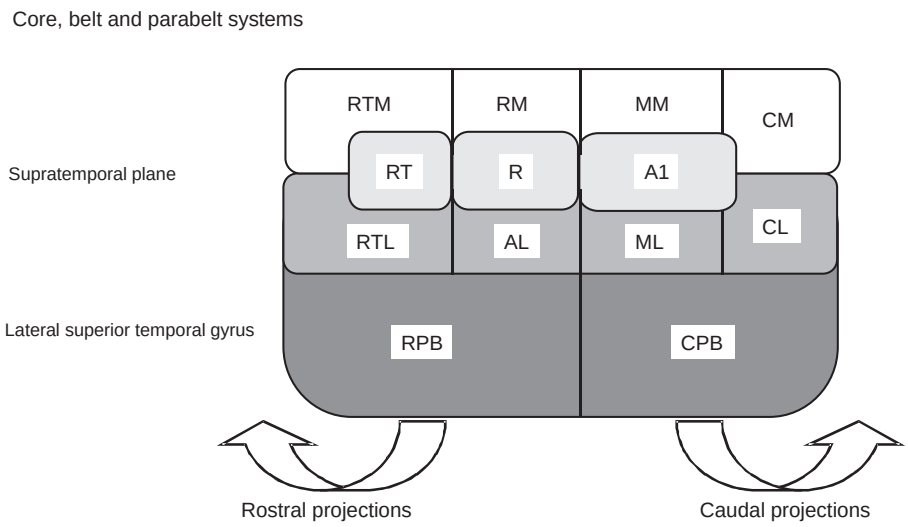

Fig. 3 Depiction of non-human primate auditory areas. There are three levels of processing, which proceeds in series and parallel. In addition to the primary core area A1, there are two additional core areas, rostral (R) and rostrotemporal (RT), distinguished by reversal of tonotopy in each area. At the second stage there are medial and lateral belt areas: medial rostrotemporal (RTM), rostromedial (RM), middle medial (MM), caudomedial (CM), caudolateral (CL), middle lateral (ML), anterolateral (AL) and rostrotemporal lateral (RTL). The third stage comprises caudal and rostral parabelt (CPB and RPB). The approximate locations in the superior temporal gyrus and the onward projections are shown.

be studied in man, many, including the author, have become convinced that the organisation of the auditory cortex of the monkey will inform speech perception in man. Over the past three decades, there has been a great expansion in our knowledge of the organisation of monkey auditory cortex. Three hierarchical levels of auditory cortex have been identified: core, belt and parabelt (Fig. 3)[25,26]. The core, primary auditory cortex, has a number of fields, distinguished by the difference in the tonotopic organisation of their neurons, *i.e.* the tuning of individual neurons to vibrations at different distances along the basement membrane of the cochlea. The response of core neurons is maximal to pure tones. The core fields receive their ascending afferents in parallel from the ventral nucleus of the medial geniculate complex (MGv), connect reciprocally with their neighbouring core field and also with their neighbouring fields in the surrounding belt cortex. The core does not project more distally to ipsilateral cortical areas. Little is known about the medial belt, as it is hidden within the lateral sulcus out of reach of the single cell recording electrode of the experimenter. However, much about the lateral belt regions is being revealed. First, they receive connections from adjacent core regions to form a second stage of auditory processing. Second, they receive a parallel input from thalamic and midbrain regions other than the primary pathway from MGv to core.

Third, they are reciprocally connected with the neighbouring parabelt regions that lie on the lateral surface of the superior temporal gyrus. The parabelt, which also receives a parallel input from thalamic and midbrain regions, forms the third stage of auditory processing. Both belt and parabelt neurons connect to more remote regions in the superior temporal gyrus and sulcus.

Although the belt neurons remain tonotopically organised, they respond more strongly to bands of noise rather than pure tones. Greater responsiveness to complex sounds is also observed in the parabelt. It has now been demonstrated that there are belt and parabelt neurons that respond strongly, and sometimes relatively specifically, to conspecific vocalisations[27,28]. Of particular interest over the past few years has been the notion that there are two or more auditory processing 'streams'[29,30]. This is analogous to the visual system, where the identity of a perceived object is processed in a ventral 'what' pathway, but where an object is in relation to the observer and other objects in the environment is processed in a dorsal 'where' pathway. The origin of the sensory information for both pathways is primary visual cortex, but subsequent divergence of information directs spatial location to posterior parietal cortex whereas information about object identity passes to more ventral locations in the parietal and temporal lobes. The identity of an auditory object and its location are signalled by temporal and spectral information in the perceived sound. Information about the identity of an object can be conveyed by one ear alone, whereas location requires two ears. Therefore, information about auditory 'what' and 'where' already diverge in sub-cortical regions. However, there is suggestive evidence that cortical processing of auditory 'what' and 'where' also occurs in the cortex. In non-primary auditory areas, the more rostral neurons respond to the sound identity of an object, evidenced by their relatively selective responses to different conspecific vocalisations, whatever the spatial position from which the call was emitted[28]. In contrast, the more caudal neurons showed greater specificity for the location of the call. This rostral-caudal distinction was, however, relative rather than absolute. A further, and compelling, line of evidence comes from anatomical studies. A combined physiological and anatomical study[31] demonstrated that the rostral lateral belt region projects to rostral and ventral prefrontal cortex (PFC), whereas caudal regions project to dorsolateral PFC. Even where there was close proximity of rostral and caudal projections to a frontal lobe region, such as in Brodmann's area 45, the rostral projections from auditory cortex lay a little more rostral to the caudal projections. Romanski and colleagues[31] speculated that dorsolateral PFC is associated with spatial processing and ventrolateral PFC is associated with object-processing. Therefore, the combination of the physiological responsiveness of auditory neurons and the different prefrontal domains to which non-primary auditory neurons project suggests at least two functionally different auditory processing streams.

The rostral and caudal streams are far from absolute, with middle belt regions sending projections to both rostral and caudal PFC. What is likely to be revealed is that there are more than two processing streams. In this context, there is a potential stream in humans that may not be present in monkeys, as their vocalisations are innate rather than learnt. Further extending the analogy from the visual system, which is capable of informing 'how', to allow reaching and grasping in visual space[32], an equivalent skill when surveying an auditory scene is to hear a sequence of sounds and then reproduce them vocally. Human infants go through stages when they learn to map the perception of culture-specific and regional-specific human vocalisations on to articulatory movements. We retain the ability to acquire new vocabulary throughout our adult lives. In addition, we are capable of mimicking the sounds of other species and of non-animate objects. Belin and Zatorre[33], in a comment, discussed auditory 'how' in relation to the movement of peak vibrations on the basilar membrane of the cochlea as complex spectrotemporal information unfolds over time: this, they argued, is equivalent to movement of light across the retina when visual objects move. This argument has been taken further, based on functional neuroimaging results in man[34,35]. These have shown a region in the supratemporal plane, at the junction with the inferior parietal lobe, that acts as a sensorimotor interface between hearing and articulating. As auditory scenes always unfold over time, and can never be re-visited in the way that is possible with eye movements around a static visual scene, posterior temporal cortex may also hold sequences of sounds in on-line, short-term memory as an articulatory plan is formulated and then rehearsed[34].

It is now becoming possible, from meta-analyses of PET and fMRI studies, to map out differential responses to simple and complex auditory stimuli in superior temporal regions[23]. There is increasing evidence that intelligible speech, both normal and noise-vocoded, activates the rostral left lateral temporal lobe when contrasted with equivalently acoustically complex, but unintelligible, sounds[36,37]. The interpretation is that this is a verbal 'what' pathway. It is linked, via the uncinate fasciculus with ventrolateral PFC. This region of the PFC has been linked with the explicit retrieval of words from memory based on a semantic cue (for reviews, see Bookheimer[11] and Poldrack *et al*.[38]). In addition to the ventrolateral PFC, an additional study has emphasised that rostral and medial PFC is engaged by controlled processing of word meaning[39].

In the light of all the new evidence, both from the research in non-human primates and from functional imaging studies in man, one can speculate about the distributed system involved in speech perception. One involves a rostral route from the anterior temporal cortex via the uncinate fasciculus to ventral and rostral PFC: the other involves a caudal route via the arcuate fasciculus to dorsolateral PFC (Fig. 4). Although these two routes are unlikely to be independent, the former may process word meaning and the

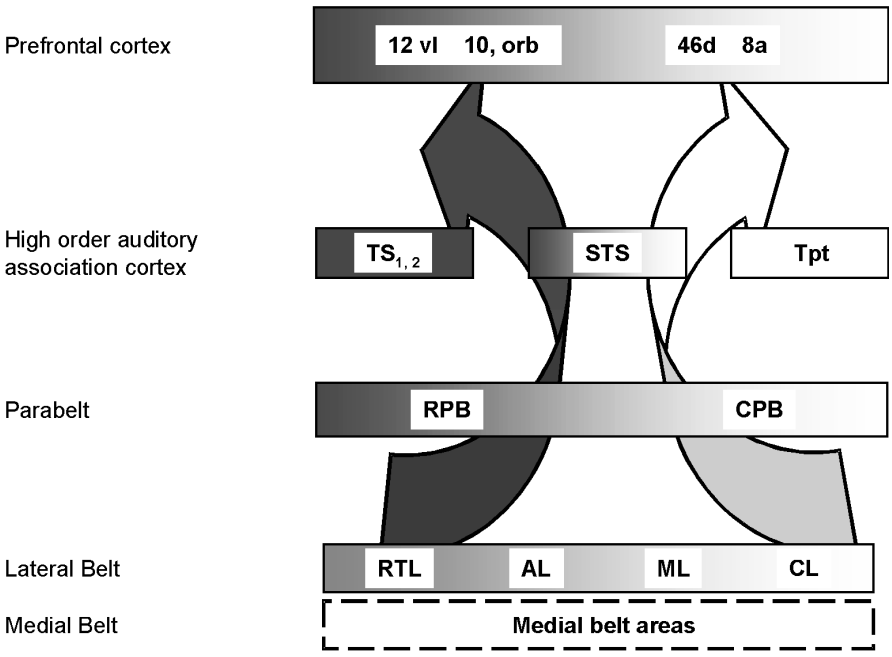

Fig. 4 Diagram of prefrontal projections of auditory areas in non-human primates. In addition to the projections within the auditory areas, already described in the caption to Figure 3, rostral belt and parabelt neurons project to the rostral superior temporal gyrus (areas TS1,2) and superior temporal sulcus (STS) and caudal belt and parabelt neurons project to the caudal superior temporal gyrus (areas Tpt) and STS. The rostral and caudal superior temporal regions also project to different prefrontal domains, indicated by their Brodmann area numbers.

latter word sound structure (phonetics and phonology). Such a synthesis fits well with meta-analyses of inferior frontal gyrus (IFG) activations in response to verbal tasks[11,38]: by-and-large, rostral and ventral PFC is activated by controlled processing of word meaning, whereas more caudal and dorsal PFC is activated by the controlled processing of the phonology of words. Although these regions lie in close proximity in the IFG, the literature on non-human primates, reviewed above, suggests that they may have quite divergent connections to the superior temporal lobe, compatible with the hypothesis that there are several, partially independent streams of speech processing in humans.

The idea that rostral temporal regions may be involved in access to word meaning does not find favour in the stroke aphasiology literature. The interpretation from left temporoparietal infarction is that access to meaning via the spoken word is via posterior temporal and inferior parietal cortex. This viewpoint is well expressed in a recent review[40]. However, evidence from the distribution of atrophy in a variant of frontotemporal dementia, semantic dementia, in which there is

progressive and profound loss of semantic knowledge, suggests that the rostral and ventral temporal lobes are critical for this form of memory[41,42]. Infarction of the anterior temporal lobe is a rare form of stroke because of the distribution of the branches of the middle cerebral artery, and so there is selection bias in the stroke literature. Much has been made of the absence of loss of spoken comprehension following left anterior lobe resection for intractable epilepsy, However, it still remains unclear what can be inferred about the normal distribution of language from patients who have experienced intractable epilepsy, with the possibility of cortical reorganisation as a consequence of the repeated epileptic discharges[43–45]. Furthermore, there is evidence from patients with semantic dementia that left anterior temporal lobe atrophy may result in progressive anomia, early evidence of semantic impairment, but profound loss of semantic knowledge is only observed when there is bilateral temporal lobe atrophy[46]. Epileptic patients do not undergo bilateral temporal lobe resections except in the famous case of HM, who demonstrated an impaired ability to acquire new knowledge as well as a profound impairment of episodic memory[47].

A recent functional neuroimaging study by my group has produced evidence that left temporoparietal infarction that involves primary auditory cortex resulted in reduced activity in the intact rostral temporal lobe in response to heard speech. Furthermore, activity in the rostral temporal lobe correlated with the degree of recovery of speech comprehension (Crinion and colleagues, submitted for publication). Such evidence suggests that the effects of posterior temporal lobe infarction produce wide-spread effects throughout the ipsilateral temporal lobe, an observation that is compatible with both rostral and caudal 'streams' of auditory processing and a partial reconciliation of the aphasic stroke and semantic dementia literature.

Localising semantic memory with functional neuroimaging

As humans develop, they not only develop greater knowledge about the world through direct experience of objects, but increasingly rely on information communicated through meaningful symbols, *i.e.* words and pictures. Furthermore, we become able to express and comprehend increasingly abstract ideas and concepts that bear little or no relation to the physical world. Thus, our ability to map words on to meaning offers us an enormous capacity to expand our knowledge beyond our immediate horizons. Long-term declarative (conscious) memory was envisaged by Tulving[48] to comprise two forms. The one for personal events and experiences, episodic memory, is related to both the time and place of acquisition. Factual (semantic) knowledge is context-independent and shared, in more or less detail, across a cultural community. As originally

envisaged, there was not only a psychological, but also a neurological, dissociation between the two forms of declarative memory, with different neural structures involved for knowledge of self and knowledge of the world. The alternative view is that episodic and semantic memory are not independent of one another, and behavioural dissociations in patients are more apparent than real[49].

Declarative memory is dependent on medial temporal lobe structures. All input to the hippocampus is channelled through the entorhinal cortex. Both the parahippocampal and perirhinal regions, which share reciprocal projections, project to entorhinal cortex and thus, indirectly, to the hippocampus. Their anatomical connections are with unimodal sensory association cortices, with perirhinal cortex only receiving sensory afferents from third-order association cortices[50].

Based on observations on patients with damage to medial temporal lobe structures, connectionist models of memory assume that long-term, well-rehearsed (*i.e.* 'consolidated') memories, whether event or factual, are stored in the neocortex. The percept of the thing or event to-be-remembered is initially processed in unimodal primary and association sensory cortex. Medial temporal structures are involved with initial encodement and early recall of memories. Over time, however, it is conceived that the medial temporal lobe structures connect neocortical neurons, distributed widely in neocortex, that represent the memory. With time and rehearsal of the memory (*i.e.* recurrent recall), the initially weak connections between the distributed local neocortical neural systems become strong and memory recall can occur more or less independently of medial temporal structures (for a discussion of these issues, see Murre *et al.*[51]).

It has long been recognised that the hippocampus is central to episodic memory encodement. Furthermore, there is evidence that bilateral hippocampal damage, sufficient to result in a severe and persistent retrograde and anterograde amnesia, does not prevent the acquisition of object knowledge, *i.e.* semantic memory[52]. However, a hypothesis is developing from results on medial temporal lobe ablation experiments in monkeys that perirhinal cortex may be strongly implicated in the acquisition of semantic memory[53,54]. Perirhinal cortex, comprising Brodmann's areas 35 and 36, surrounds the entorhinal cortex on all but its medial side, the junction between the two lying in the rhinal sulcus. In the macaque monkey, it extends laterally into the inferior temporal gyrus, and lies medial to high-order unimodal visual cortex (area TE). Its distribution is similar in humans, but it probably extends laterally over the anterior part of the fusiform gyrus (a gyrus that is absent, or at least small, in monkeys)[50]. Similarly, in the human it would seem likely that the parahippocampal **area** spreads lateral to the parahippocampal gyrus, into the mid-fusiform gyrus. There are now a number of functional neuroimaging studies using verbal stimuli that have activated

ventromedial temporal lobe structures, either the left parahippocampal gyrus and/or fusiform gyrus. At least two studies have suggested that the activation is bilateral[55,56]. Unfortunately, many language activation studies may underestimate the amount of ventromedial temporal lobe involvement. This is because the choice of baseline task is critical to observe an activation in this region[57] and because the signal-to-noise ratio in this region is fMRI studies is relatively weak.

Many other studies have adopted a different strategy, which is to investigate category-specific effects. One of our studies illustrates the activations within multimodal temporal cortex associated with speech comprehension (Fig. 5). In contrast, the many studies that have investigated activations associated with decisions about words or pictures relative to the semantic category to which they belong reveal signal in various parts of visual association cortex (for a comprehensive review of this large literature, see Martin & Chao[58]). These have been interpreted, for example, as processing shape and colour for living kinds and motion for tools. Additional regions may also be activated, such as motor-related cortex for tools. The distribution of category-specific activations are most easily interpreted as

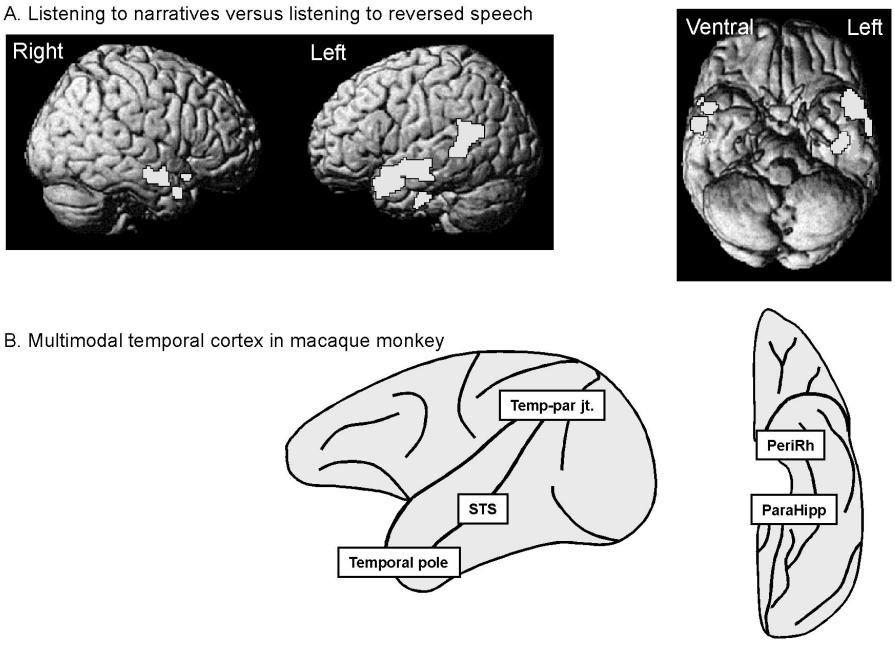

Fig. 5 The top panels demonstrate the distribution of activations in the contrast of listening to speech with listening to acoustically complex but unintelligible reversed speech, projected on to surface MR renderings of the brain surface (SPM99, Wellcome Department of Cognitive Neurology). The activations lie within or close to multimodal temporal cortex, assuming the distribution of these cortical areas are similar to those worked out with precision in the macaque monkey (lower panels). Temp-par jt., temporoparietal junction; STS, superior temporal sulcus; PeriRh, perirhinal cortex; ParaHipp, parahippocampal area.

object concepts being represented within neocortex that was engaged when the various sensory and motor attributes of the object were being acquired. There are, however, other theories about how there may be categorical organisation within the semantic system[59]. Nor does it explain how abstract concepts (*e.g.* the difference between *charity* and *altruism)* are organised. What is becoming apparent is that although the 'semantic system' is normally represented as a single black box in information processing models of language, complex, multidimensional memories cannot be localised in the same manner as sensory modalities, such as colour and visual motion. In functional imaging studies, it is the processes rather than the representations that may generate the greatest signal, which goes some way to explain the ease with which a signal can be obtained in the left inferior frontal gyrus during the controlled processing of any aspect of lexical memories.

The production of speech

Unlike speech perception, there is no parallel between animal vocalisations and speech production. Although the acquisition of song by hatchling songbirds is compared with the acquisition of language by human infants[19], it is difficult to infer the anatomy of human speech from the neuroanatomy of birds. There have been very few studies of normal speech production using functional neuroimaging. Two recent publications, although somewhat different in design, produced converging results[60,61]. Both propositional and non-propositional speech were observed to activate bilateral motor-related regions (including sub-cortical regions and the cerebellum) and the supplementary speech area. In addition, there were three left-lateralised cortical areas in parts of Wernicke's and Broca's area: at the temporoparietal junction, the anterior insula and the frontal operculum. These regions appear to be involved in the preparation and execution of articulation. In addition, propositional contrasted with non-propositional speech demonstrated a distributed, predominantly left-lateralised, extrasylvian neural system (Fig. 6), although the processes that these may represent are many, including the on-line retrieval of semantic and episodic memories and the construction of sentences with the correct syntactic structure. There was a very prominent rostral left PFC activation, which has a clinical correlate in the sparse speech production observed in patients who have had left anterior cerebral artery territory infarction.

Left dorsolateral frontal activation during spontaneous speech was restricted to the rostral part of the frontal operculum, and did not extend widely into the dorsolateral PFC and rostral cingulate/paracingulate cortex as observed in controlled word retrieval, such as verbal fluency. This may well reflect a marked difference in working memory demands between ordinary speech and controlled word retrieval.

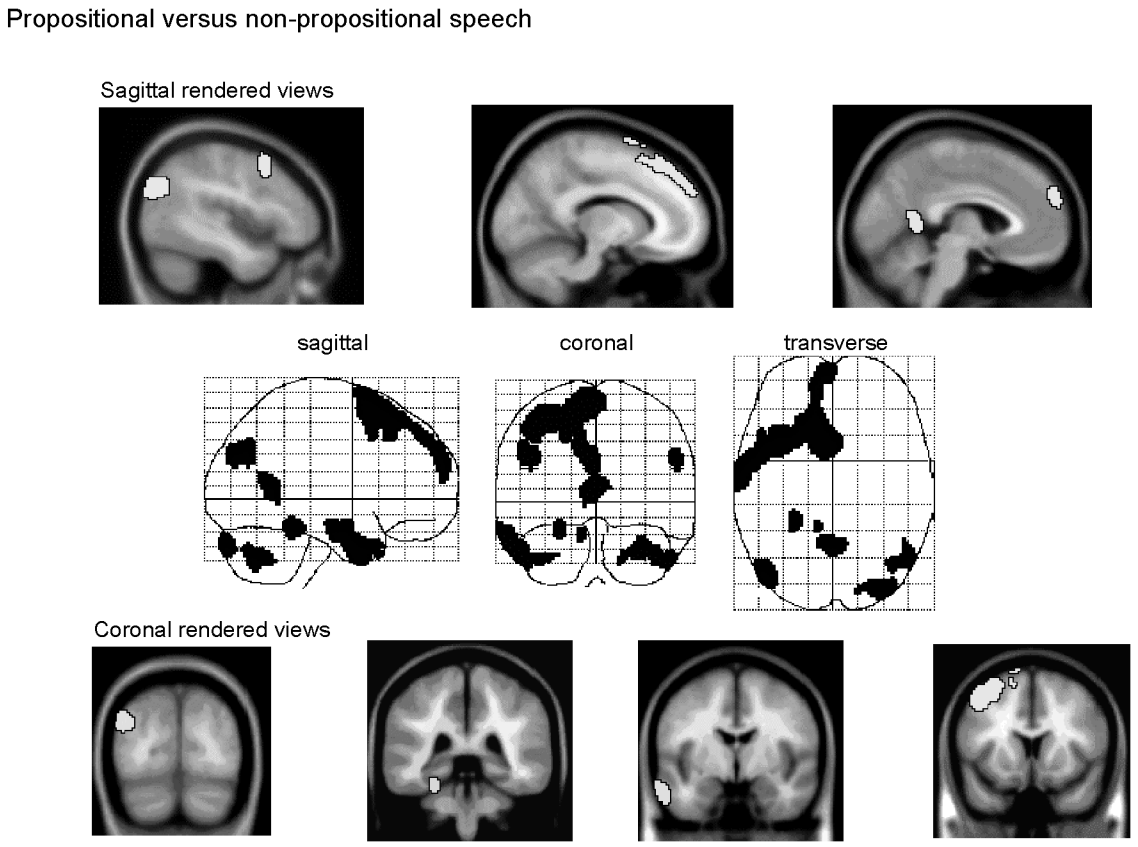

Fig. 6 Distribution of activations in the contrast of normal (propositional) speech with counting and recitation (non-propositional speech). Whole brain projections (centre panels) are supplemented by renderings of the activations on sagittal and coronal mean MR image slices taken from a panel of normal subjects (SPM99, Wellcome Department of Cognitive Neurology). The contrast shows widely distributed activations in extrasylvian cortex, particularly prominent in rostral prefrontal cortex.

Studies on aphasic patients

Studies of 'resting' markers of diseased human brain function, using tracers that measure regional cerebral blood flow, oxygen consumption, glucose metabolism, inflammation or radioligand binding have been widely implemented. There is a whole discipline dedicated to modelling the fate of administered tracers, so that regional radioactivity can be interpreted reliably as, for example, the absolute glucose metabolism of a brain region or the binding potential of dopamine-D_2 receptors in the striatum. These studies, directed at investigating molecular and biochemical markers of brain pathology, are very different conceptually from the functional activation mapping with PET and fMRI, although combining both radioligand binding and functional activation in a patient group may have great potential[62].

Our ideas of recovery from aphasic stroke have changed little over the past 150 years. These encompass three basic hypotheses. The first is that there is recovery of tissue around the edge of the lesion, the residual tissue being able to support the impaired behaviour, more or less, because of redundancy within the local neural system. The second proposes that there is transfer of the lost function to homotopic cortex in the right cerebral hemisphere. The third makes the common-sense suggestion that, under certain circumstances, patients adopt strategies to circumvent the lost function. An example of such a strategy is the use of overt or covert letter-by-letter reading and reversed spelling to identify a word after a left occipital lesion destroys the acquired ability to read words as whole units. The operation of one or both of the first two postulated mechanisms have motivated almost all of the functional imaging studies of aphasic recovery to date. One or more of the three mechanisms underlie, explicitly or implicitly, attempts to rehabilitate aphasic patients. In terms of drug treatment, the vast majority of research has gone into attempts to salvage the so-called penumbra of potentially viable tissue around the edge of a recent infarct. This has been attempted either by thrombolytic therapy to encourage early reperfusion or by use of one of many, but so far unlicensed, neuroprotective agents. Early reperfusion has certainly been shown to reverse an aphasic deficit[63]. Behavioural treatment may work by 'retraining' neural systems ipsilateral or contralateral to the lesion, or direct the patient to develop strategies to overcome the deficit. And yet, the types of behavioural treatment attempted in a clinical setting are rarely informed by any direct evidence of the changes in brain function that they are supposed to induce.

Therefore, the potential value of functional activation studies in the study of aphasia is evident. The best might be a serial study, to look at changes over time following the stroke, particularly if it includes an investigation into the functional effects of behavioural or drug therapy, either acutely or chronically. Nevertheless, the problems inherent in studying patients are many, which explains the few activation studies to date on aphasic patients compared to the very many that have attempted to study language processes in normal subjects.

It is self-evident that a decision has to be made at the outset about what language disorder is to be investigated in a particular study. Whatever disorder is chosen, patients with other stroke syndromes will be excluded and, therefore, after other exclusion criteria are taken into account, less than 5% of new stroke admissions may be eligible for the study. Thus, stroke may be common, but patients for a specific functional imaging study may be few and far between. The second consideration is whether patients are to be grouped on the basis of the behavioural deficit or on the location of the lesion. The latter makes more sense when one bears in mind that aphasic syndromes and location of lesions correlate rather poorly[10]. Even if

patients are to be grouped on lesion location there is the problem that no two vascular events are precisely alike in terms of anatomical distribution. Most importantly, not only will the cortical extent of the lesions differ between patients, but there will be differential involvement of underlying white matter, manifesting as changes in function of intact, remote but anatomically and functionally connected regions.

Perhaps the most contentious issue is how much emphasis should be placed on distinguishing between controlled and automatic mental processing, from ideas formally developed in psychology in the 1970s. Controlled processes are those that require the conscious focusing of attention on the mental task. They are of limited capacity and the processing of information for task execution proceeds serially: thus controlled task performance precludes the ability to perform a second, unrelated task at the same time. In practice, most controlled tasks used in language activation studies make heavy demands on working memory. By contrast, automatic processing does not require the conscious focusing of attention, it does not limit capacity and parallel processing is possible. Speech perception and production are largely automatic.

Two studies from the same group illustrate many of these points. The first was a study by Rosen and colleagues[64]. They investigated the hypothesis that one of two mechanisms might explain recovery from aphasic stroke. The first was that right hemisphere regions were responsible for recovery. The second proposed that early after left hemisphere infarction there was loss of function in intact left hemisphere language regions that subsequently recovered. The study was based on patients with chronic lesions, more than 6 months after the ictus. These patients were selected on a neurological rather than behavioural criterion: they all had a single cerebral infarct that encompassed the left inferior frontal gyrus, including the operculum, and the underlying white matter. Only six patients out of a stroke population of 300 met the necessary criteria. Unavoidably, the total extent of infarction was very variable across the six patients.

Having defined a hypothesis and a patient group, the strategy adopted was to use a behavioural activation task known to activate the left inferior frontal gyrus. The task employed was word-stem completion: a visual presentation of three letters was followed by the subject completing the letter triplet to form a word (*e.g. cou* to *couple* or *count*). This requires controlled processing. Lexical retrieval under such circumstances is based on the orthographic/phonological structure of words, the meaning of the retrieved word being irrelevant to the task demand. Thus, the task requires the temporary retrieval and storage of known words that are appropriate to the task demand and the cue. In English, a language with many-to-many correspondences between the written and pronounced form, strategy may influence the observed activation pattern. Thus, *cou* is pronounced

differently in *count* and *couple,* and a subject may use an orthographic strategy alone or an othographic-to-phonological strategy, such as only searching for words in which *cou* is pronounced '*cow*'. Activations associated with verbal working memory have been the subject of many functional neuroimaging studies, with regional specialisation within different regions of the PFC[65]. What is unknown is whether working memory processes, decision-making, response selection and monitoring of the response have much to do with the normal use of language to communicate, and how the results may shed light on the processes underlying the ability to re-establish communication after an aphasic stroke. At a bed-side clinical level, there is no evidence that a patient's ability to communicate is reliably indicated by his or her score on a test of word-stem completion. This is equally true of verbal fluency, which is commonly used by clinical neuropsychologists to probe left dorsolateral PFC function in the *absence* of an aphasic deficit[9].

Nevertheless, studying recovery of the ability to do verbal problem-solving tasks may indirectly index recovery of the ability to communicate in normal speech, and the results may be clinically valuable. However, there remains another problem. Inevitably, in the study of Rosen and colleagues there was an overall difference in the behavioural performance of patients compared to normal controls. This may result in two difficulties with interpretation. First, if reaction times are longer in the patients, then the degree of task-dependent activity, but not its distribution, may be significantly greater in the patients compared to the normal controls: a consequence of the length of time the processes required for task performance are engaged. The sum of this greater neural 'work' is reflected in a larger local increase in local blood flow, the so-called time-on-task effect. Second, task accuracy may influence the results by the demands it makes on parallel processes. Thus, the right dorsolateral PFC has been associated with response monitoring in verbally-based tasks. Both absolute accuracy and the subject's estimation of their confidence in the accuracy of their response, measures that are probably not independent, influence activity in right dorsolateral PFC[66]. Importantly, less accuracy and reduced confidence are associated with greater activity. Thus, a patient group who make more errors, and are less confident of their responses, may activate self-monitoring systems in the right dorsolateral PFC more than the normal group, a reflection of behavioural impairment and not recovery.

Therefore, if the two hemispheres are performing two independent but related functions, and activity is not only dependent on task accuracy and/or speed but is inversely related in different regions, then interpretation of the data becomes problematic. Furthermore, the study demonstrated that four out of eight normal subjects showed evidence of left *and* right PFC activation during task performance. Nevertheless, the patients activated the right PFC to a significantly greater degree. The authors

argued that this task-by-group interaction demonstrated a *qualitative* difference in the function of the right DLPFC between the two groups and not, as had been argued in a previous study by Warburton and colleagues[67], which had used verbal fluency as the activation task, only a *quantitative* difference. Clearly, if the right PFC activity observed in half the normal controls and most of the patients indexed monitoring of response, whereas left PFC activity indexed processes involved in the retrieval of words into working memory, then Warburton and colleagues were right.

In response to a failure to correlate performance by the patients on word-stem completion with right IFG activity in the first study, the same group from St Louis used a word-stem completion task that was repeated on familiar stimuli[68]. They argued that the right PFC activation in their earlier study did not necessarily indicate a 'take-over' of function by the right frontal lobe for a process that was executed by the left frontal lobe prior to the stroke. This may indeed be the case, as argued above, although the authors discussed this possibility in more general terms of 'effort' or 'epiphenomenal'. They argued that a repetition priming effect, indexed by a reduction in activity when repeatedly performing the task on familiar stimuli, would demonstrate direct involvement of that region in the task. This may indeed be true. However, as everyday speech comprehension and production is so automatic, it is not clear how observing repetition priming in a demanding metalinguistic task will inform hypotheses about the mechanisms of recovery of *normal* language function.

As it is, this study was somewhat cavalier about anatomical localisation. The critical issue was the location of the right 'dorsal IFG' activation in patients that showed decreasing activity with repeated word-stem completion on the same stimuli. Its anatomical co-ordinates place it in the posterior part of the precentral gyrus, close to primary motor cortex but just anterior to it in premotor cortex. This location was >2.5 cm posterior and dorsal to the co-ordinates of either of the two peaks of right frontal activity described in the earlier study by Rosen and colleagues. However, even if it were assumed that such a posterior activation in the right frontal lobe was associated with a cognitive rather than motor process, its significance is open to other explanations. As the patients became more practised with repeated word-stem stimuli their error rate reduced. This was in contrast with the normal controls, whose success on the task was at or close to ceiling. Thus, self-monitoring, and confidence in the accuracy, of responses by normal subjects, may have been low even when confronting novel stimuli, whereas in patients monitoring may have declined with increasing stereotypy of response associated with repeated exposure to the same stimuli.

The outcome of this detailed nit-picking is to conclude that, whatever the merits of the two studies from the St Louis group, their approach permits many potential re-interpretations. It is apparent that the use of problem-solving tasks may create a rod for the investigator's back. This is not the

popular view. Psychological investigation has a long tradition of requiring a subject to respond to a stimulus. As it is the reaction times and errors which are the measures from which conclusions are drawn, this approach is the only one that allows experimentation. We appear not to have fully adapted to the notion that we now have an independent physiological measurement of brain function in response to behaviour. There is still a demand to 'know what the subject is doing' while being scanned, and to have measures to 'prove' that they were paying attention during, for example, listening to speech. However, everyday communication is over-practised and, for the most part, effortless. Many of the processes associated with speech perception are pre-attentive, and understanding of familiar words is so automatic that, as the old saw has it, one cannot help thinking of a pink pachyderm when told: 'whatever you do, don't think of a pink elephant'.

In terms of processes associated with word retrieval, there is much to commend investigating normal speech production, as this is when word retrieval is associated with communication. Clear behavioural measures of performance are then available to the experimenter, in terms of the rates of production of all words or specific classes of word, the rhythm of the speech, *etc*. However, to do so is to sacrifice precision: speech production, from the formulation of a message to articulation, is not going to allow an assignment of one function to each activated brain region.

It is clearly easier to judge the relevance to recovery of a region activated in patients if activity within the region correlates with a measure of language competence. Thus, activity measured during repetition of single words correlated with measures on a test of speech comprehension[69,70]. One difficulty here is that it is not transparent why a measure of speech comprehension should directly relate to activity within brain regions involved in repetition: patients with transcortical sensory aphasia have normal repetition but very impaired speech comprehension. Furthermore, one of our recent studies (Blank and colleagues, submitted for publication) which demonstrated a clear difference (a cross-over interaction) between normal subjects and patients with infarction of the left frontal operculum in the activation of the **right** frontal operculum, showed no correlation between various measures of speech production and activity in the *right* frontal operculum. This may be for the trivial reason that neural activity was simply 'on', in an all-or-none fashion, in this region when speech was attempted. An alternative is that the contribution of the right opercular system to speech production in the patients depended on connections with left hemisphere systems undamaged by the infarct. Interruption of white matter tracts by the left frontal infarct may have influenced cross-hemisphere functional connectivity in a manner that was not reflected in activity in the right frontal operculum.

There have been very few studies on the effects of therapy on aphasic recovery. The best known is the acute effects of behavioural retraining

on right posterior temporal function in four patients with left hemisphere infarction[71]. The retraining took place between individual scans, and activity in the homologue of Wernicke's area increased with an improvement in comprehension. Support comes from the observation that there is also spontaneous (untrained) change in right posterior temporal function after Wernicke's area infarction[72]. A methodological problem is that non-specific time effects are often observed in a series of functional images, and it remains a problem to disambiguate genuine treatment effects from these time effects.

Concluding remarks

To date, functional imaging studies on aphasic stroke and its potential treatment have been limited to a very small number of patients. This will

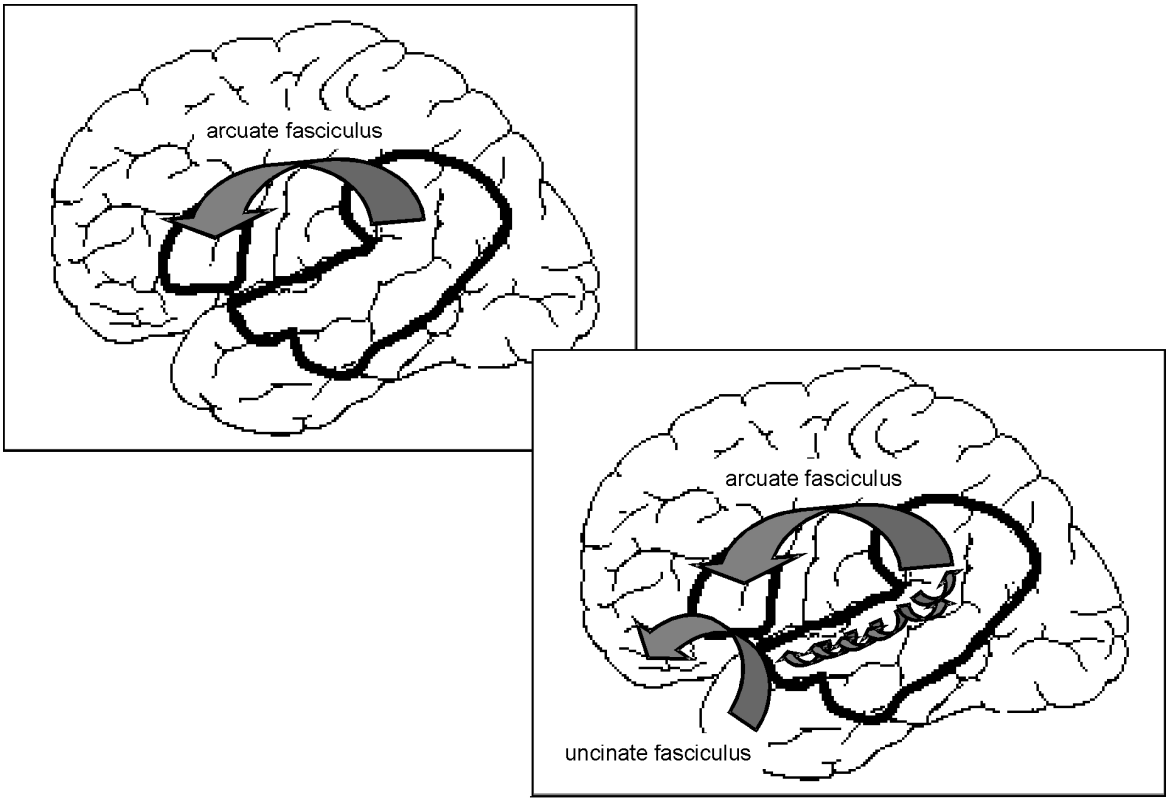

Fig. 7 Diagram of the old neurological model of language (top left) with an ill-defined Wernicke's area connected via the arcuate fasciculus to Broca's area. A more realistic, but still much simplified, model (bottom right) shows rostral and caudal projections along superior temporal cortex, with two projections to the prefrontal cortex via the arcuate and uncinate fasciculi. All projections are shown as unidirectional, but there are an equal number of forward and back projections.

change. The combination of new observations on auditory processing in non-human primates and functional imaging studies in normal subjects during speech perception is producing a fundamental shift away from the standard neurological model of language: Wernicke's area (with an uncertain boundary) connected to Broca's area by the arcuate fasciculus (Fig. 7). High order unimodal and multimodal sensory association temporal lobe regions are under the influence of both 'bottom up' (from sensory cortex) and 'top down' (from PFC) processes. Therefore, the observed activity of an intact region, previously functionally connected to an infarcted area downstream, may change, depending on whether a behavioural task emphasises 'bottom up' or 'top down' processes[73]. The effects of behavioural and drug treatments, designed to enhance one or other modulatory inputs into the region, will give direct evidence of the potential efficacy of the treatment.

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