The estimated prevalence of aphasia in the UK and the USA is 250 000 and 1 000 000, respectively. The commonest aetiology is stroke. The impairment may improve with behavioural therapy, and trials using cortical stimulation or pharmacotherapy are undergoing proof-of-principle investigation, but with mixed results. Aphasia is a heterogeneous syndrome, and the simple classifications according to the Broca-Wernicke-Lichtheim model inadequately describe the diverse communication difficulties with which patients may present. Greater knowledge of how intact neural networks promote recovery after aphasic stroke, either spontaneously or in response to interventions, will result in clearer hypotheses about how to improve the treatment of aphasia. Twenty-five years ago, a pioneering study on healthy participants heralded the introduction of functional neuroimaging to the study of mechanisms of recovery from aphasia. Over the ensuing decades, such studies have been interpreted as supporting one of three hypotheses, which are not mutually exclusive. The first two predate the introduction of functional neuroimaging: that recovery is the consequence of the reconstitution of domain-specific language systems in tissue around the lesion (the ‘perilesional’ hypothesis), or by homotopic cortex in the contralateral hemisphere (the ‘laterality-shift’ hypothesis). The third is that loss of transcallosal inhibition to contralateral homotopic cortex hinders recovery (the ‘disinhibition’ hypothesis). These different hypotheses at times give conflicting views about rehabilitative intervention; for example, should one attempt to activate or inhibit a contralateral homotopic region with cortical stimulation techniques to promote recovery? This review proposes that although the functional imaging data are statistically valid in most cases, their interpretation has often favoured one explanation while ignoring plausible alternatives. In our view, this is particularly evident when recovery is attributed to activity in ‘language networks’ occupying sites not observed in healthy participants. In this review we will argue that much of the distribution of what has often been interpreted as language-specific activity, particularly in midline and contralateral cortical regions, is an upregulation of activity in intact domain-general systems for cognitive control and attention, responding in a task-dependent manner to the increased ‘effort’ when damaged downstream domain-specific language networks are impaired. We further propose that it is an inability fully to activate these systems that may result in suboptimal recovery in some patients. Interpretation of the data in terms of activity in domain-general networks affords insights into novel approaches to rehabilitation.

**Keywords:** aphasia; functional brain mapping; functional recovery; cognitive control; attention

**Abbreviations:** ACC = anterior cingulate cortex; IFG = inferior frontal gyrus; SFG = superior frontal gyrus; STS = superior temporal sulcus
Introduction

It is claimed that one-third of all stroke patients have an aphasic deficit as part of their presenting symptoms (Laska et al., 2001; Pedersen et al., 2004; Lazar et al., 2008). Although half of these patients recover much or all of their language function, the remainder are left with a persisting and disabling impairment of communication. It is estimated that in the USA and the UK alone, the current prevalence of post-stroke aphasia is 1 million and 250,000, respectively.

Not surprisingly, most studies and subsequent meta-analyses that have investigated prognosis have concluded that the initial severity of the overall stroke deficit, and of the aphasic deficit specifically, and the size of the lesion afford the most reliable indicators of prognosis (Pedersen et al., 1995; Lazar et al., 2008; Maas et al., 2012; Plowman et al., 2012). However, these factors explain only about one-third of the variability in recovery from aphasia, with lesion volume contributing little to the variance in one multiple regression analysis on 22 patients (Lazar et al., 2008). The contribution of demographic factors, such as sex, age, premorbid intelligence and handedness, as explanatory variables for prognosis appears to contribute even less to the prediction of final outcome (Plowman et al., 2012); although in one large series it has been demonstrated that increasing age is associated with a worse prognosis (Knoflach et al., 2012). Periodically it is reported that infarction of certain small regions reliably result in a specific and lasting aphasic deficit, but such reports may attract further studies suggesting that the anatomical-behavioural association is not as strong as originally suggested (for example, see Dronkers, studies suggesting that the anatomical-behavioural association is that infarction of certain small regions reliably result in a specific deficit as part of their presenting symptoms (Laska et al., 2001; Pedersen et al., 2004; Lazar et al., 2008). Although half of these patients recover much or all of their language function, the remainder are left with a persisting and disabling impairment of communication. It is estimated that in the USA and the UK alone, the current prevalence of post-stroke aphasia is 1 million and 250,000, respectively.

The introduction of functional neuroimaging to language research

The modern era of functional neuroimaging was heralded by a publication in Nature (Petersen et al., 1988), now cited ~2000 times. This reported a study on healthy participants using PET and what became the classic ‘subtraction’ design, whereby activity in one behavioural state is subtracted from another to identify the anatomical location of the cognitive function of interest. Two semantic tasks were reported as showing a conjunction of activity in the left inferior frontal gyrus (IFG). The authors concluded that the left IFG, largely incorporating ‘classic’ Broca’s area [Brodmann areas (BA) 44 and 45] and adjacent ventrolateral inferior frontal cortex, ‘participates in processing for semantic association’. In the discussion of this result, the authors explicitly contrasted their result with the neurological model of single word processing proposed by Geschwind (1965a, b), who argued that the processing of semantic associations is located at the other extreme of the left sylvian fissure, in inferior parietal cortex.

The paper of Petersen and colleagues (1988), and a further publication by the same group (Petersen et al., 1990), were very influential in terms of introducing a new methodology to human neuroscience and advancing our understanding of the functional anatomy of language. However, most would now agree that one plausible interpretation of their studies, that representations of semantic knowledge are stored in the left IFG, is an unlikely explanation for their results. Semantic processing is likely to be very distributed, with anterior and ventral temporal cortex playing a key role (McClelland and Rogers, 2003; Acosta-Cabronero et al., 2011; Lambon Ralph et al., 2012). What has become evident is that the left IFG is a core component in processes involved in accessing these representations in a context-dependent manner. Therefore, alternative proposals were made based on further experiments, using the alternative (and now almost universal) methodology of functional MRI: for example, that it is not the retrieval of semantic knowledge per se that results in increased left IFG activity, but rather selection of information amongst competing alternatives from semantic memory (Thompson-Schill et al., 1997); or, alternatively, that the left IFG controls semantic retrieval irrespective of whether the selection is

This review will consider the role of functional neuroimaging in fulfilling this goal. One strong conclusion that we will draw is that interpretation of the data has often been too narrow. In particular, we build on prior evidence from parallel studies in the field of cognitive neuroscience that have often been overlooked in the field of aphasiology, drawing attention to the contribution of domain-general systems acting on damaged domain-specific language networks. In essence this is a refinement of a common bedside clinical intuition; that if executive function and attention are impaired in an aphasic patient, due to the lesion distribution or co-existing age-related cognitive decline, microangiopathic cerebrovascular disease or neurodegenerative disease, the worse the prognosis and the response to rehabilitative interventions.

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from amongst competing representations (Wagner et al., 2001). As another example, an interpretation based on retrieval processes rather than on representations was also made in relation to the effects of semantic ambiguity in sentence comprehension. Thus, ‘the shell was fired towards the tank’ is effortlessly accepted as meaningful, despite the two nouns and the verb having a number of alternative meanings. Were a listener to select incorrectly from among these alternative meanings, the sentence would be perceived as nonsensical. When participants in a functional MRI study parsed ‘high-ambiguity’ sentences, they demonstrated increased left IFG activity compared to when they heard ‘low-ambiguity’ sentences, comprised of words with only one meaning that were otherwise matched for linguistic variables, such as word frequency and imageability (Rodd, 2005).

Interpretations of the function of Broca’s area have continued as a major preoccupation of functional neuroimaging research [entering the search terms ‘Broca’s AND (fMRI OR PET)’ in PubMed returns 731 references]. Given its pre-eminence as a cortical ‘module’ for language, most functional neuroimaging research directed at this region has been by scientists who are preoccupied with the processing of phonology, words or syntax, and how separable subcomponents of Broca’s area are involved in these different linguistic processes (Vigneau et al., 2006). Nevertheless, activity in Broca’s area has also come to feature prominently in studies that have hypotheses and interpretations unrelated to language-specific processing. Broca’s area is anatomically and neurochemically heterogeneous (Amunts et al., 1999; Amunts and Zilles, 2012). Further, the anatomical and functional connectivity of this region is widely distributed (Lemaire et al., 2013), particularly if one views Broca’s area as including not only the pars opercularis and triangularis, but also the adjacent lateral orbital, ventral premotor and anterior insular cortices, various combinations of which appear in publications referring to Broca’s area (Fig. 1). It is, therefore, not surprising that this region activates in response to non-linguistic as well as linguistic stimuli. Thus, for example, this region figures prominently in a functional MRI study that investigated the processing of the hierarchical organization of behaviour (Koechlin and Jubault, 2006). Humans have the capacity to combine sequences of subordinate stimuli into increasingly complex superordinate structures, which in turn influence the behaviour of the observer. This occurs across multiple domains (for example, playing chess or listening to a passage of music); and, of course, also during the processing of language, when a sequence from a limited repertoire of phonemes can be used by the speaker to elicit emotions and actions in the listener. Koechlin and Jubault’s (2006) study demonstrated that both the left and right IFG were implicated in the ‘chunking’ of, and responding in a rule-based manner to, sequences of visual stimuli, with a posterior-to-anterior gradient for simpler and more complex sequences. The bilateral response in this study is of interest, as the comprehension and production of language are typically only associated with increased activity in the left IFG (Hickok and Poeppel, 2007), suggesting that hierarchical sequencing of the elements of language carried out in the IFG (otherwise known as ‘unification’, see Hagoort, 2005) has become the property of a domain-specific and lateralized subsystem embedded within a more bilateral domain-general network.

Broca’s area, through its anatomical and functional connectivity, may be involved in a number of processes engaged in the comprehension and production of single words and sentences. However its functional heterogeneity has been demonstrated in a further functional MRI study on healthy participants. This set out to determine the response of the left pars opercularis and triangularis across a wide range of language and non-language tasks. Within these two regions, although subcomponents were active only during a language task, others were active across all tasks (Fedorenko et al., 2012).

The additional observation in the study of Fedorenko and colleagues (2012) was that the harder a task, the greater the activity in Broca’s area. Often, activity associated with task difficulty, as reflected in the reaction times and/or error rates, has been considered a confound when the motivation for a study is to determine the functional anatomy of domain-specific processes. Dealing with this confound can be achieved, at least in part, in several ways: ensuring that in a subtraction design the activation and baseline tasks are matched for reaction times and/or error rates; failing that, by regressing out these variables in the analysis; or, if the study was an event-related functional MRI study, simply by discarding the functional

![Figure 1](https://academic.oup.com/brain/article-abstract/137/10/2632/2846855/br/13771082632864665) Downloaded from https://academic.oup.com/brain/article-abstract/137/10/2632/2846855 by Queensland University of Technology user on 30 August 2019
images from the trials with prolonged reaction times or error rates. Occasionally, researchers have included the activity associated with task difficulty (sometimes known as the ‘time-on-task’ effect) alongside their main findings. One example of such a publication, and of interest in terms of the rest of this review, is that by Binder and colleagues (2005). The study investigated the functional anatomy of domain-specific representations for concepts conveyed by abstract compared to concrete words. The healthy participants performed a lexical decision task on concrete, abstract words and non-words (the last being the baseline condition). The length of the reaction times for making the decision were: non-words > abstract words > concrete words. In the main analyses, the reaction times were included in the regression model to account for any effect of time-on-task in the main result. However, an analysis investigating the effect of reaction times across all trials was also included. This analysis demonstrated positive correlation between reaction times and distributed activity in regions including bilateral anterior insular cortices and the adjacent IFG (anterior insular/IFG), the middle frontal gyri, extending posteriorly to the precentral sulci and the intraparietal sulci, dorsal anterior cingulate cortex (ACC) and adjacent superior frontal gyrus (dorsal ACC/SFG) (Fig. 2). These regions form two networks, the cingulo-opercular and one of several fronto-parietal networks, that have now been studied in some form two networks, the cingulo-opercular and one of several superior frontal gyrus (dorsal ACC/SFG) (Fox, 2005; Vincent et al., 2007). These intrinsic networks have been variously named as ‘task positive’ (Seeley et al., 2007), or a ‘task control’ network (Dosenbach et al., 2007). These are sometimes further divided into subnetworks including ‘fronto-parietal control’, ‘dorsal attention’, and ‘cingulo-opercular’ (Dosenbach et al., 2007; Vincent et al., 2012). Occasional researchers have included the activity associated with task difficulty (sometimes known as the ‘time-on-task’ effect) along-side their main findings. One example of such a publication, and of interest in terms of the rest of this review, is that by Binder and colleagues (2005). The study investigated the functional anatomy of domain-specific representations for concepts conveyed by abstract compared to concrete words. The healthy participants performed a lexical decision task on concrete, abstract words and non-words (the last being the baseline condition). The length of the reaction times for making the decision were: non-words > abstract words > concrete words. In the main analyses, the reaction times were included in the regression model to account for any effect of time-on-task in the main result. However, an analysis investigating the effect of reaction times across all trials was also included. This analysis demonstrated positive correlation between reaction times and distributed activity in regions including bilateral anterior insular cortices and the adjacent IFG (anterior insular/IFG), the middle frontal gyri, extending posteriorly to the precentral sulci and the intraparietal sulci, dorsal anterior cingulate cortex (ACC) and adjacent superior frontal gyrus (dorsal ACC/SFG) (Fig. 2). These regions form two networks, the cingulo-opercular and one of several fronto-parietal networks, that have now been studied in some form two networks, the cingulo-opercular and one of several superior frontal gyrus (dorsal ACC/SFG) (Fig. 2). These regions are now considered to be components of the domain-general networks, they are known as cingulo-opercular and fronto-parietal control networks, and it is proposed that these networks are responsible for processes associated with domain-general cognitive control and attention.

Domain-general cognitive control brain systems

The human brain contains cortical regions that are specialized for domain-specific processes: for example, early visual or auditory processing, orthographical perception or motion perception. However, over the past decade there has been considerable research on domain-general brain systems that are engaged across a wide range of cognitive tasks.

The existence of domain-general cortical regions is reasonably well established. One influential hypothesis is that a set of these regions, termed the ‘Multiple-Demand’ system, rapidly adapt to exert top–down control during a broad range of tasks (Duncan and Owen, 2000; Duncan, 2010, 2013; Fedorenko et al., 2013). The Multiple-Demand system relates to general psychological constructs like intelligence quotient, cognitive flexibility, behavioural inhibition, and attentional control (Duncan, 2005; Hampshire et al., 2012). This system is minimally engaged when performing an overlearned (habitual) task, but comes into play when solving novel problems, when task conditions change and habitual responses require modification, and more generally, whenever tasks require a greater level of top–down control. One can conceptualize that language tasks may engage all of these processes, particularly when domain-specific resources alone do not suffice, either in healthy participants performing difficult metalinguistic tasks (Hampshire et al., 2013) or when the habitual functioning of language networks have been impaired by pathology.

The regions in the Multiple-Demand system include bilateral intraparietal sulcus, inferior frontal sulcus, anterior insula and adjacent frontal operculum, and the presupplementary motor area and adjacent dorsal anterior cingulate cortex (SMA/dorsal ACC). The regions in the Multiple-Demand cortex have been further fractionated by some authors into subcomponents (Hampshire and Owen, 2006; Hampshire et al., 2012). Depending on the exact task demands, these regions activate to varying degrees; however, the same subregions commonly co-vary in activation levels across tasks (Hampshire et al., 2012) and even across time during rest (Dosenbach et al., 2007). These intrinsic networks have been variously named as ‘task positive’ (Fox, 2005), ‘task-activation ensemble’ (Seeley et al., 2007), or a ‘task control’ network (Dosenbach et al., 2007). These are sometimes further divided into subnetworks including ‘fronto-parietal control’, ‘dorsal attention’, and ‘cingulo-opercular’ (Dosenbach et al., 2007; Vincent et al., 2012).
The exact mental processes that are mediated by these domain-general cortical and subcortical systems have not yet been clearly defined (Hampshire et al., 2012). Similarly the use of over-specified labels may fail to capture the broader contributions of these networks to domain-general control. We will now briefly describe these networks (also see Fig. 3).

A combination of co-activation of cortical regions that overlap with the Multiple-Demand system is termed by some as the ‘fronto-parietal control’ (Dosenbach et al., 2007, 2008; Power et al., 2011; Power and Petersen, 2013) or ‘executive control’ network (Seeley et al., 2007). This network incorporates left and right anterior and dorsolateral prefrontal cortices and the intraparietal sulci/adjacent dorsal inferior parietal cortices. The activity in the fronto-parietal control system has been attributed to initiation of task performance, and adjustment of cognitive control on a continuing trial-by-trial basis.

The ‘dorsal attention network’ (DAN), includes occipitotemporal cortex, the superior parietal lobule, intraparietal sulcus and frontal eye field in each hemisphere. Activity in this region has been mainly studied using goal-directed top–down selection of visual stimuli based on internal goals and shifts of spatial attention (Corbetta and Shulman, 2002; Corbetta et al., 2008; Vincent et al., 2008). This is in contrast to a predominantly right-lateralized ‘ventral attention network’ that also incorporates the junction of the inferior parietal lobe with posterior temporal cortex. This system is engaged in stimulus driven attention and detects salient and behaviourally relevant stimuli (Corbetta and Shulman, 2002; Corbetta et al., 2008; Singh-Curry and Husain, 2009). These two networks overlap spatially with a set of regions implicated in processes that require attention sustained over time. Regions in both these networks have been proposed to work together during tasks that depend on vigilant attention (Langner and Eickhoff, 2013). However, the exact processes that they support remain the topic of much debate.

The co-activation of a network of brain regions in the dorsal ACC and adjacent medial superior frontal gyrus (dorsal ACC/SFG) and bilateral anterior insular and adjacent inferior frontal gyrus has been termed the cingulo-opercular network (Dosenbach et al., 2007, 2008; Power et al., 2011; Power and Petersen, 2013). The co-activation of a similar set of regions have been termed the ‘salience system’ (Seeley et al., 2007; Menon and Uddin, 2010). These regions can co-activate with the regions in the fronto-parietal control network (Vincent et al., 2008). The activity in this network has been attributed to goal-directed behaviour through the stable maintenance of task sets, or detection of salient events. In this review we adopt the label, cingulo-opercular network that focuses on anatomical description rather than the more controversial process-based labels (e.g. salience network).

We will now focus in more detail in one region that has been observed to be active in many language studies, and that is part of the domain-general cingulo-opercular network, namely the dorsal ACC/SFG (Braun et al., 1997; Warburton et al., 1999; Blank et al., 2002; Geranmayeh et al., 2012; Price, 2012). In addition to language tasks, this region is activated by many non-linguistic cognitive tasks, such as processing of emotion, pain, attention, motor control, memory, reward, and the monitoring of responses and errors (Paus, 2001; Rushworth et al., 2003; Ridderinkhof, 2004; Kennerley et al., 2006; Alexander and Brown, 2011; Torta and Cauda, 2011; Levstad et al., 2012). It remains unclear the amount to which the responses to these very disparate stimuli are processed by a common systems or by anatomically overlapping but functionally distinct subsystems within the dorsal ACC/SFG (Torta and Cauda, 2011). However, a small number of functional...
MRI studies on healthy participants have study designs that allowed the investigators to explicitly dissociate language-specific functional MRI activity from that related to domain-general processes involving the cingulo-opercular network. These studies and their results are summarized in Table 1.

We describe two of these studies in more detail. Vaden et al. (2013) tested the prediction that elevated cingulo-opercular activity increases the likelihood of immediate correct word recognition. The participants were required to repeat heard words presented against a background of babble noise. The signal-to-noise ratio during speech perception had two levels, so that one repetition task was more difficult and resulted in greater errors. Activity in the cingulo-opercular network increased during the trials with lower signal-to-noise ratio, and activity in this system correlated with error rates across all trials. Further, using partial correlations functional connectivity analyses on each trial, the authors demonstrated that increased cingulo-opercular activity was predictive of better word-recognition performance on the next trial. In a second study, Piai et al. (2013) required their subjects to perform three tasks, each with two or three levels of difficulty. Two tasks involved verbal stimuli and responses while the third was a visual task with manual responses (Table 1). Reaction times and errors were longer for the more difficult levels of each task. Activity in the dorsal ACC was increased across all tasks, and in two of the three tasks activity was significantly greater during the more difficult trials.

Unlike the networks described above that activate during ‘exteroceptive’, externally driven tasks, the Default Mode Network (Fig. 3) is an ‘interoceptive’ system with a distinct and reproducible anatomical distribution (Raichle et al., 2001; Esposito et al., 2006; McKiernan et al., 2006; Buckner et al., 2008). It includes midline cortex, located in the ventral anterior and posterior cingulate cortex and the precuneus, but also lateral neocortical regions, the angular gyri (posterior inferior parietal cortices) and rostral dorsolateral prefrontal cortex, and the medial temporal lobes (Fig. 3). Although typically considered a resting state network, part of this network overlaps with those supporting speech production and the semantic processing of verbal stimuli (Seghier et al., 2010; Geranmayeh et al., 2012; Seghier and Price, 2012; Smith et al., 2012). Binder et al. (2009) argue that during ‘rest’ human brains are far from inactive, with stimulus-independent thoughts engaging the retrieval of both episodic and semantic memories, and that this function explains activation of components of the Default Mode Network during language processing.

The exteroceptive or task-positive networks demonstrate anticorrelated activity with the interoceptive Default Mode Network (Fox, 2005; Spreng et al., 2010). The balance between the two has been studied in healthy participants (Weissman et al., 2006; Kelly et al., 2008; Leech et al., 2011), and it is now apparent that this balance becomes disrupted during pathological conditions. This has been demonstrated in traumatic brain injury (Bonneille et al., 2011), Alzheimer’s disease (Zhou et al., 2010), and brain changes during normal ageing (Andrews-Hanna et al., 2007).

These observations are also relevant to stroke. A cerebral hemispheric stroke may be a focal disease of acute onset, but in addition to damage to a limited (albeit often large) region of cortex, it also invariably results in damage to white matter tracts, including long intra- and interhemispheric pathways. It also often includes highly connected subcortical nuclei. The contributions of ‘disconnection syndromes’ to the behavioural consequences of stroke are well recognized (Geschwind, 1965a, b; Catani, 2005) but those of ageing, microangiopathic cerebrovascular disease as the result of co-existing hypertension and diabetes, and unsuspected neurodegenerative pathology are difficult to assess in individual cases. It is intuitive that these will have an adverse effect on stroke recovery and rehabilitation. This may, in turn, depend on the distributed connectivity between the exteroceptive and interoceptive networks, and hence efficient task-related deactivation of the Default Mode Network, a concept that is entering the literature on the cognitive effects of cerebrovascular disease (Sheorajpanday et al., 2013; Tuladhar et al., 2013).

This role of domain-general networks in recovery from aphasic stroke is becoming recognized in the neuropsychological literature. Although most of the neuropsychological studies on aphasia recovery design their assessments and consider their results in terms of residual function in domain-specific language systems, there is a small literature that has associated communication problems in patients with aphasia with associated impairments of executive control (Robertson and Murre, 1999; Purdy, 2002; Fillingham et al., 2006; Fridriksson et al., 2006; Lambon Ralph et al., 2010; Murray, 2012), attention (Murray, 2000, 2012; Lambon Ralph et al., 2010), problem-solving as measured by Raven’s Coloured Matrices and Wisconsin Card Sorting Test (Gainotti et al., 1986; Baldo et al., 2005), memory (Swinburn et al., 2005; Fillingham et al., 2006; Lambon Ralph et al., 2010; Murray, 2012), semantic control (Corbett et al., 2009), or the ability to inhibit distracting stimuli (Wiener et al., 2004). These non-linguistic verbal cognitive problems seem to have an impact on the response to behavioural therapy (Goldenberg et al., 1994; Robertson and Murre, 1999; Fillingham et al., 2006; Lambon Ralph et al., 2010; Yeung and Law, 2010). Thus, for example, in a study on 33 patients with chronic post-stroke aphasia and naming difficulties (Lambon Ralph et al., 2010), a principle component analysis revealed both a phonological factor and a cognitive factor as best predicting therapy outcome designed to improve the residual anoma.

Suggested proposals about mechanisms of language recovery after a stroke

Functional neuroimaging studies investigating aphasia recovery usually interpret their results in the context of three broad mechanisms. The first two predate the introduction of functional neuroimaging. The ‘perilesional’ hypothesis proposes that recovery is the consequence of the reconstitution of domain-specific language systems in the tissue around the lesion (Heiss et al., 1999; Warburton et al., 1999; Rosen et al., 2000; Hills et al., 2006; Winhuisen et al., 2007; Meiner and Breitenstein, 2008; Szafarski et al., 2013). The second, the ‘laterality-shift’ hypothesis, is that recovery is attributable to a ‘shift’ of language function to the homotopic cortex in the contralateral hemisphere (Musso
Table 1 Functional MRI studies on healthy participants that explicitly dissociated language-specific functional MRI activity from that related to non-linguistic or domain-general processes

| Task [number of levels of task difficulty] | Outcome | Reported MNI coordinates of activity in regions associated with the cingulo-opercular network (x,y,z) |
|------------------------------------------|---------|---------------------------------------------------------------------------------------------------|
| Visual attention: Eriksen Flanker task [two] | The same frontal regions (ACC, R aI/IFG, R dIPFC) were engaged, regardless of task. Activity in these regions increased with task difficulty. | Visual task −3.45,18 | Visual task 39.3, −3 | − |
| Single word recognition: repeating heard filtered words [four] | | Language task 9,27,30 | Language task 30,21,9 | − |
| Repeating heard sentences [two: vocoded versus clear sentences] | The difficult verbal task was associated with activity in the cingulo-opercular network. Parts of this network (dorsal ACC/SFG and left aI/IFG) also showed increased activity as the non-verbal task became more difficult. This activity was attributed to domain-general cognitive control. | −6.17,49 | 33.23,1 | −30.23, −2 |
| Non-speech sound amplitude discrimination using button responses [seven] | | | |
| Three tasks (stimuli were presented in two domains: written and heard words): | Right pars opercularis responded to non-linguistic perceptual processing. | −3.33,39 | 36.21, −6 | −42.21, −6 |
| Perceptual manipulation judgement: detect pitch or font size change | | | |
| Semantic judgement | There was greater activity in regions in a cingulo-opercular network for the perceptually manipulated stimuli during the perceptual processing but not phonological or semantic processing. | | | |
| Phonological judgement | Activity in the left and right anterior insulae, was present for all three decision tasks on all stimuli relative to 'rest'. | | | |
| Repeating words that were heard over background babble [two] | Activity in the cingulo-opercular network increased in proportion to percentage errors and task difficulty. Elevated cingulo-opercular activity increases the likelihood of immediate correct word recognition. | −7.31,40 | 42.27, −10 | −42.24, −4 |
| Vocal picture naming whilst ignoring visual distractors [three] | All three tasks showed activity in the dACC, in the contrast of difficult trials (incongruent) against rest baseline. | −1.35,34 | 43.21, −9 | − |
| Vocal colour naming while ignoring visual distractors (Stroop task) [Three] | In the two language tasks, this area showed increased activity for the difficult (incongruent) relative to easier (congruent) stimuli, consistent with the involvement of domain-general mechanisms of attentional control in word production. | −4.12,36 | − | − |
| Non-language task (Simons task) [two] | | | |

In all these studies activity was related to non-linguistic processing in components of the cingulo-opercular network (Fig. 5B).
Abbreviations are: dACC, dorsal anterior cingulate; aI/IFG, anterior insula/inferior frontal gyrus; dIPFC, dorsolateral prefrontal cortex; R, right; L, left; MNI, Montreal Neurological Institute stereotactic co-ordinates.
et al., 1999; Blasi et al., 2002; Leff et al., 2002; Winhuisen et al., 2005; Saur et al., 2006; Turkeltaub et al., 2012). The third, the ‘disinhibition’ hypothesis, has come out of functional neuroimaging research. It proposes that right-sided activity is the product of loss of transcallosal inhibition. It is further proposed that this contributes little to recovery, and may even hinder it by reciprocal inhibition of any remaining undamaged tissue in the left hemisphere (Belin et al., 1996; Rosen et al., 2000; Blank et al., 2003; Naeser et al., 2004, 2005; Thiel et al., 2006).

A hierarchy for aphasia recovery has been proposed (Heiss and Thiel, 2006) that attempts to incorporate these disparate findings. On their synthesis, the best recovery is achieved by the restoration of the original activation patterns within the network of the dominant hemisphere, which is less likely after large lesions. Compensation may also involve secondary centres of the ipsilateral network, a less efficient reorganization. If most of the ipsilateral perisylvian cortex is infarcted, the least efficient compensation is mediated by homotopic contralesional regions. However, conflicting opinions about the roles of ‘laterality shift’ and ‘transcallosal disinhibition’ result in opposing views about rehabilitative interventions; for example, should one attempt to activate or inhibit a contralateral homotopic region with cortical stimulation techniques to promote recovery?

Consideration is rarely given in these proposals to the influence of intact domain-general networks on recovery, or the possibility that some of the ‘abnormal’ activity recorded in post-stroke aphasia is the result of the upregulation of normal activity within domain-general networks (Wise, 2003). Thus, activity in response to a language task observed at the margins of a lesion that has affected Broca’s area, or in the homologous region, may not reflect partial domain-specific recovery, but be attributable to activity within intact components of the domain-general cingulopercular system. Further, the greatest activity may be observed in the right homologue of Broca’s area in those patients who have shown the least recovery because they have the greatest difficulty with tasks performance, and not because this reflects an ‘inefficient’ domain-specific system for recovery (Naeser et al., 2005). Despite an increasing number of published studies that have investigated aphasia using functional neuroimaging in the last decade, the proportion of these studies that correlate recovery with domain-general cognitive processes has remained constant, even though an extensive parallel literature has emerged on these domain-general systems over this period (Fig. 4). In the next sections we will suggest a re-interpretation of specific examples from amongst published studies; but, of course, separating activity in domain-specific from that in domain-general networks is not straightforward without explicit adaptation of study designs, something that has only been performed in a few studies.

**Interpreting task-induced activations in contralateral cortex following left hemisphere lesions**

There are earlier studies, using non-neuroimaging techniques and a variety of patient populations that have implicated the right hemisphere in recovery of language-specific functions (Kinsbourne, 1971; Gazzaniga, 1983; Gazzaniga et al., 1984; Papanicolaou et al., 1988; Vargha-Khadem et al., 1997). There have been additional reports of right-handed patients who
had recovered some language function after a left hemisphere aphasic stroke, but who then deteriorated further after a second stroke affecting the right hemisphere (Barlow, 1877; Gowers, 1887; Lee et al., 1984; Basso et al., 1989; Cappa and Vallar, 1992; Turkeltaub et al., 2012). However, single-case studies or case series on a few patients are rarely conclusive.

Interpretation of functional neuroimaging studies has not, as yet, allowed a consensus to be reached about the function of the right hemisphere in recovery (Price and Crinion, 2005; Crinion and Leff, 2007). A recent meta-analysis concluded that aphasic patients consistently activated spared left hemisphere language nodes, adjacent left hemisphere cortical regions, and right hemisphere homotopic regions (Turkeltaub et al., 2011). Patients with left inferior frontal lesions recruited right IFG more reliably than those without. It was considered that some regions, including right dorsal pars opercularis, were functionally homologous with corresponding areas in control subjects, whereas others, including right pars triangularis, were functionally dissimilar.

There have been other studies that have used brain stimulation techniques, with or without functional neuroimaging, and have reported a supportive role for the right hemisphere in language recovery after a left hemisphere infarct (Winhuisen et al., 2005, 2007) or gliomas (Thiel et al., 1989) or gliomas (Thiel et al., 1989; Lee et al., 1987; Turkeltaub et al., 2011). Patients with left inferior frontal lesions recruited right IFG more reliably than those without. It was considered that some regions, including right dorsal pars opercularis, were functionally homologous with corresponding areas in control subjects, whereas others, including right pars triangularis, were functionally dissimilar.

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it to a dynamic language-specific process contributing to recovery from aphasia after stroke. In contrast, the alternative interpretation was adopted by authors of a study that related right IFG activity in aphasic patients to non-linguistic processing due to task difficulty or learning (van Oers et al., 2010).

It could be argued that inferring participants’ cognitive ‘effort’ across time in the study of Saur et al. (2006) is speculative, whereas the language scores provide objective behavioural data. However, the study went further in relating regional activity with an out-of-scanner composite language score achieved by the patients. At the time of the first study, the language score correlated strongly with activity in both the left and right anterior insular/IFG. Further, the improvement in language scores between the acute and second scans correlated with activity in the right anterior insular/IFG and a midline frontal region that, on the coordinates supplied, locates to the dorsal ACC/SFG (Fig. 5A, yellow peaks on the sagittal slice). Although a contribution from language-specific networks to this result is possible, which was the

Figure 5 Activation peaks from the neuroimaging studies of language tasks discussed in the text that can be attributed to domain-general systems. Each activation peak is represented as a sphere with a 5 mm radius around the reported peak coordinate of activity, superimposed on a single T1-weighted magnetic resonance image, anatomically normalized into the Montreal Neurological Institute standard stereotactic space. (A) Activation peaks from studies on patients with stroke that showed a positive correlation with measures of aphasic recovery. These peaks localized to the dorsal anterior cingulate cortex (sagittal view) and right IFG/right anterior insula (axial views). The red regions lie within the ‘cingulo-opercular’ network described by Dosenbach et al. (2007). Yellow, purple and green regions are from the studies of Saur et al. (2006), Brownset et al. (2014), and Raboyeau et al. (2008), respectively. (B) Activation peaks from studies on healthy participants that explicitly dissociated language-specific functional MRI activity from that related to domain-general processes. In all these studies activity was related to domain-general processing in components of the cingulo-opercular network. Red region represents peak activity in the ‘cingulo-opercular’ network described by Dosenbach et al. (2007). Blue represents activation peaks from studies listed in Table 1. (C) Activation peak (yellow) in the right posterior STS from the study on stroke patients with left posterior temporal infarction by Leff et al. (2002). In that study increased activity in the right posterior STS was attributed to a ‘shift’ of language function from the left to the right posterior STS, and was attributed to the recovery of word comprehension. This region is just inferior to the right temporoparietal junction that is engaged in attentional processes. Red represents convergent of activity in the right temporoparietal junction related to vigilant attention from a meta-analysis of attentional neuroimaging studies by Langner and Eickhoff (2013). A = anterior; P = posterior; L = left; R = right.
established technique (Sharp had been manipulated to reduce spectral information, using an /C24 repeat that sentence immediately afterwards. They achieved
patients were required to listen to a sentence in preparation to repeat that sentence immediately afterwards. They achieved
~60% accuracy as a group. The healthy control subjects performed the same task, except that in some trials the sentences had been manipulated to reduce spectral information, using an established technique (Sharp et al., 2009; see also a meta-analysis by Adank, 2012). When contrasting listening to the perceptually difficult sentences with the clear sentences in the healthy participants, they clearly demonstrated increased activity in the cingulo-opercular network, which therefore related to task difficulty but not language processing (which must have been greater during perception of the normal sentences). In patients, activity in the dorsal ACC/SFG was observed when they listened and prepared to repeat normal sentences, a task that they found difficult, and this activity correlated with performance on an out-of-scanner overt picture description task. The study was interpreted as demonstrating the influence of domain-general control when task difficulty increased, as the result of perceptual distortion of the stimuli in the healthy participants and aphasic impairment in the patients; and that the individual ability to activate this network influenced outcome after stroke.

In addition to domain-general executive networks, evidence is now emerging from patient studies and neurostimulation of healthy participants, for the existence of controlled access to semantic representations. Contrasting aphasic stroke patients with ‘semantic aphasia’ and patients with the semantic variant of fronto-temporal dementia, indicated that seemingly similar impairments are the result of impaired task-dependent access to semantic representations in the former group and degradation of the representations themselves in the latter group (Jefferies, 2006). The distribution of major pathology in the two groups is quite different, with left fronto-parietal destruction in the stroke patients and bilateral anterior temporal lobe atrophy in the patients with semantic dementia. It is suggested that executive control over semantic processing is dependent on a distributed neural network that includes bilateral dorsolateral prefrontal cortex, the left angular gyrus and left posterior temporal cortex (Thompson-Schill et al., 1997; Wagner et al., 2001; Whitney et al., 2011, 2012; Noonan et al., 2013). This evidence converges with our view on the interpretation of many of the results coming from functional neuroimaging studies.

‘Laterality shifts’ in temporo-parietal cortex

Most studies of aphasia recovery that relate recovery to ‘laterality shifts’ of language processing have reported these changes in the inferior frontal cortex. Many fewer studies have reported a similar laterality shift in the other eponymous language region, namely Wernicke’s area in left posterior temporal cortex and adjacent inferior parietal cortex (for examples see Leff et al., 2002; Teki et al., 2013). Although the evidence from lesion studies strongly implicates the left posterior temporal cortex in language processing, a recent functional-anatomical model has proposed that the acoustic analysis of heard speech and lexical access is a function of both the left and right posterior temporal cortex (albeit with a ‘weak left hemisphere bias’) (Hickok and Poeppel, 2007). This model proposes that the language processes that are strongly left-lateralized either decode meaning conveyed by the syntactical structuring and ordering of words to access sentence-level semantics or are central to speech production. On this basis, it might be expected that the homologue of Wernicke’s area can support at least some of the functions associated with the spectrotemporal analysis of heard speech and access to lexical representations. One study in support of this view was that of Leff et al. (2002), who demonstrated that the response of the right posterior superior temporal sulcus (STS) changed after chronic aphasic stroke, showing a profile that came to resemble that of the left posterior STS in healthy right-handed subjects. It was proposed that this was due to a reorganization of synaptic function in a domain-specific language. Although this interpretation may be correct, and many consider that the perception as opposed to the production of language is left-lateralized (Hickok and Poeppel, 2007), it is a region just inferior to the right temporoparietal junction, at the intersection of the posterior end of the STS with the inferior parietal lobule and the lateral occipital cortex (Fig. 5C). A meta-analysis of 55 studies has concluded that the right temporo-parietal junction forms part of a distributed network of brain regions mediating vigilant attention (Langner and Eickhoff, 2013). This network consists of top-down and bottom-up attentional processes, and overlaps with other fronto-parietal components of the ventral attentional system (Fig. 3) that respond to salient and behaviourally relevant stimuli (Corbetta and Shulman, 2002; Corbetta 2008). In the model proposed by Langner and Eickhoff (2013), the right temporoparietal junction may be engaged in ‘reorienta
tion signalling’ and become active when attention has drifted away from the task and needs to be refocused. Thus, a response at the posterior end of the right STS that is greater in aphasic patients than in healthy control subjects as they listen to verbal stimuli could plausibly reflect differences in the degree of engagement of the ‘bottom-up’ attentional processes rather than a change in the response of language-specific cortex. This again addresses the issue that aphasic patients and healthy controls differ not only in terms of language processing, but also in the demands on attention and executive control, with aphasic patients almost invariably having to exert increased attention and cognitive control when processing verbal stimuli and perform linguistic tasks.
Interpreting training induced changes following aphasic stroke

With the exception of the earlier discussion on neurostimulation-induced changes in aphasic stroke, we have so far mainly focused on the brain responses to spontaneous recovery after aphasic stroke. Functional neuroimaging has also been used to investigate training-induced recovery (Musso et al., 1999; Cherney and Small, 2006; Fridriksson et al., 2006; Thompson et al., 2010). However, these studies have included few patients (i.e. <4) (Cherney and Small, 2006; Fridriksson et al., 2006; Meinzer et al., 2007; Vitali et al., 2007) or larger case-series of patients analysed individually (Musso et al., 1999; Meinzer et al., 2008; Thompson et al., 2010), which makes generalization of their findings to the larger population unreliable.

To our knowledge only two studies have looked at training-induced effects using a group level analysis, and both of these have emphasized the role of systems supporting language rather than shift of language function per se. Raboyeau et al. (2008) studied the effect of lexical training on 10 patients performing a naming task in their native language compared directly with 20 healthy participants completing the same task in a foreign language. They found an increase in activity in the right anterior insular/IFG after training in both groups. The activity in the right anterior insular/IFG correlated with behavioural improvement in patients (see Fig. 5A, green sphere on axial slices) whereas the activity in a right dorsal ACC region correlated with behavioural improvement in both groups. There was also a post-training deactivation in the regions associated with the Default Mode Network, suggesting that all participants were engaging more in the task. The authors interpreted these findings as a neural correlate of lexical learning and suggested that it ‘illustrates the specific monitoring role of the attention network in resolving verbal conflict’. However, the second study (Brownsett et al., 2014), found no neural correlates of training. The authors studied both healthy participants and patients with aphasia while they undertook auditory discrimination training. The authors suggested that this null result may have been due to the use of conventional univariate statistical analyses, which may be too insensitive to reveal the training-induced functional changes. Further neuroimaging studies investigating training induced changes in domain-general brain networks are needed to explore the influence of these networks on training induced recovery after aphasic stroke.

Practical implications for future study designs

In the absence of valid animal models, the study of recovery of speech and language following aphasic stroke has either to rely on clinical studies or depend on studies on healthy participants and the modulatory effects of task difficulty or the effects of non-invasive brain stimulation. To combat some of the pitfalls in interpreting functional neuroimaging signals in future studies, a few methodological issues need to be considered when designing experiments.

First is the selection of appropriate baseline tasks. Two points need to be taken into account when selecting these tasks: one is an inclusion of an equally demanding ‘non-linguistic’ baseline task. Ideally, this task should match the language task in terms of difficulty as measured by similarities in error rates and reaction times. This is needed in order to help differentiate activations resulting from linguistic networks from domain-general networks. Examples in which this issue was considered include the studies on healthy participants by Eckert et al. (2009) and Piai et al. (2013) (Table 1). Another issue when interpreting baseline tasks includes the likely modulation of activity in the Default Mode Network. As activity in the Default Mode Network is upregulated during ‘rest’ conditions, many now consider that ‘rest’ or other ‘passive’ conditions have limitations as a baseline condition for subtractive experimental designs that investigate language processing, and incorporate a higher-level baseline task (Spitsyna et al., 2006; Awad et al., 2007).

The second issue relates to the comparative task difficulty of the language task(s) between the aphasic patient group and the healthy control subjects. It has been suggested that this can only be achieved by performing functional neuroimaging studies on patient populations who are able to do a task with comparable error rates and reaction times to the control population (Price and Friston, 1999). This has its obvious limitations, and will exclude a disproportionate number of even relatively mildly affected subjects from a study. As a result, it is a restriction that has clearly been ignored in almost all patient studies. An alternative is to make the same task more difficult for the control participants. Although this may be achieved in speech comprehension paradigms (Sharp et al., 2009; Brownsett et al., 2014), it is more difficult to do in speech production paradigms. Nevertheless attempts have been made to this effect by comparing activations in controls naming objects in a partially learnt foreign language and aphasic patients naming objects (Raboyeau et al., 2008). To emphasize, measuring activity across a range of levels of task difficulty in patients and in control participants may allow the level of difficulty to be matched, and the effect of cognitive control distinguished from language-specific factors.

Third, is the need for longitudinal imaging studies of spontaneous aphasic stroke recovery. To date, only a few studies, on a small number of patients, have performed longitudinal functional neuroimaging studies in aphasic patients from the acute to chronic stage (Heiss et al., 1999; Saur et al., 2006). One limitation of longitudinal studies is the potential for alterations in vascular reactivity throughout the brain acutely after stroke. It may be necessary to measure the vascular reactivity, using, for example, a short breath-hold functional MRI task to observe the response to mild hypercarbia to prove that the lack of activation in stroke patients is not just due to a lack of neurovascular decoupling (Murphy et al., 2011). An application of a similar method was made by van Oers et al. (2010), and at least in the chronic phase (>1 year after stroke) this methodological issue seems not to be a confound.

Fourth, multivariate imaging techniques, such as independent component analysis (ICA) (Beckmann and Smith, 2004, 2005),
may identify functionally distinct but anatomically overlapping networks that are not always apparent from a subtractive univariate analysis (Leech et al., 2011, 2012; Geranmayeh et al., 2012). ICA takes advantage of low frequency fluctuations in the functional MRI data to separate the signal into spatially distinct components that will include domain-general and domain-specific cognitive networks (Smith et al., 2009). As an example from our own research (Geranmayeh et al., 2012), a simple univariate contrast between participants speaking and generating non-communicative movements of the articulators failed to demonstrate any activity in the left parietal cortex; in fact, if anything, net activity within this region was less than in the baseline condition. However, an analysis using ICA demonstrated that within the left inferior parietal cortex there was a locally distributed subcomponent whose activity correlated strongly with that in both the left IFG (Broca’s area) and left posterior temporal cortex (the other well-known eponymous language region, Wernicke’s area), both regions evident in the univariate analysis.

ICA is emerging as a powerful tool for separating multiple brain networks in healthy controls and patient groups (Filippini et al., 2009; Veer, 2010; Basile et al., 2013; Smith et al., 2013, 2014; Tuladhar et al., 2013). A methodological caveat is that the effects of large lesions, such as stroke, on the validity of multivariate analyses, remains to be investigated.

Conclusion

This review has argued that the interpretations of functional neuroimaging studies on aphasic stroke recovery often ignore the contribution of upregulated intact domain-general cognitive control systems, and their possible modulation of downstream domain-specific networks. With this in mind, the proposed, and at times conflicting, hypotheses about the mechanisms of language recovery after stroke may need revision, particularly when future studies are designed specifically to assign activity to domain-specific and domain-general networks. This is not just of academic interest. Stroke mostly occurs in subjects over 60 years of age, when age-related cognitive decline or presymptomatic neurodegenerative pathology is becoming established, and long-standing chronic conditions, such as hypertension and diabetes, have affected the microvasculature of the brain. Within this context, an aphasic stroke is acute focal pathology in addition to established diffuse chronic pathology. Many relatively underpowered studies have indicated that age may not affect prognosis after stroke (Plowman et al., 2012), but evidence from a very large stroke registry has concluded that age has a strong influence on outcomes (Knofflach et al., 2012). Although the mechanisms underlying this observation are not apparent from this study, one obvious factor is the effect of accumulated impairment of domain-general, distributed brain networks over the lifetime of any individual patient. This interpretation would suggest that rehabilitation should be aimed at improving function in attention and executive function as much as restoring, as far as possible, language-specific processes.

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