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### Authors

Riès, Stéphanie K  
Dronkers, Nina F  
Knight, Robert T

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## Choosing words: left hemisphere, right hemisphere, or both? Perspective on the lateralization of word retrieval

Stephanie K. Ries<sup>1,2</sup>, Nina F. Dronkers<sup>2,3,4</sup>, and Robert T. Knight<sup>1</sup>

<sup>1</sup>Department of Psychology and Helen Wills Neuroscience Institute, University of California, Berkeley, Berkeley, California

<sup>2</sup>Center for Aphasia and Related Disorders, Veterans Affairs Northern California Health Care System, Martinez, California

<sup>3</sup>Department of Neurology, University of California, Davis, Davis, California

<sup>4</sup>Neurolinguistics Laboratory, National Research University Higher School of Economics, Moscow, Russian Federation

### Abstract

Language is considered to be one of the most lateralized human brain functions. Left hemisphere dominance for language has been consistently confirmed in clinical and experimental settings and constitutes one of the main axioms of neurology and neuroscience. However, functional neuroimaging studies are finding that the right hemisphere also plays a role in diverse language functions. Critically, the right hemisphere may also compensate for the loss or degradation of language functions following extensive stroke-induced damage to the left hemisphere. Here, we review studies that focus on our ability to choose words as we speak. Although fluidly performed in individuals with intact language, this process is routinely compromised in aphasic patients. We suggest that parceling word retrieval into its sub-processes—lexical activation and lexical selection—and examining which of these can be compensated for after left hemisphere stroke can advance the understanding of the lateralization of word retrieval in speech production. In particular, the domain-general nature of the brain regions associated with each process may be a helpful indicator of the right hemisphere's propensity for compensation.

### Keywords

hemispheric lateralization; word retrieval; language production; stroke-induced aphasia; compensatory mechanisms

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Address for correspondence: Stephanie K. Ries, Ph.D., University of California, 132 Barker Hall, Berkeley, CA 94720-3190. ; Email: stephanie.ries@berkeley.edu.

### Conflicts of interest

The authors declare no conflicts of interest.

## Introduction

Language is left lateralized in 95–99% of right-handed individuals and about 70% of left-handed individuals.<sup>1</sup> Perhaps an even more striking testament of the left hemisphere dominance for language is that crossed aphasia, a language disorder due to a right hemisphere lesion in right handers, occurs in only 1–13% of individuals.<sup>2</sup>

Historically, language was the first human brain function found to contradict Bichat's law of symmetry, which assumed the symmetrical representation of brain function over the left and right cerebral hemispheres.<sup>a</sup> In the 1860s, independent reports by Paul Broca and Gustave Dax indicated that speech output processes (i.e., referred to as “articulated language”) appeared to be left lateralized.<sup>b,5,6</sup> The left lateralization of language functioning was then extended to language comprehension by Wernicke, who showed a lesion in the superior left temporal lobe could be associated with a loss of what was referred to as “speech-specific sound images”.<sup>7</sup> The association of language functioning with the left hemisphere has been prevalent ever since these findings were reported and constitutes one of the axioms of modern neurology and neuroscience.

In this review, we focus on a process that is core to our ability to produce language: conceptually driven word retrieval, which allows us to retrieve words from long-term memory as we speak. In individuals with normal language, this process is remarkably efficient, enabling adult speakers to produce two to four words per second, selected from 50,000 to 100,000 words in the mental lexicon, and erring no more than once or twice every 1,000 words.<sup>8</sup> This is, however, not the case in people with aphasia, who represent approximately 1 million people in the United States, according to the National Institute of Neurological Disorders and Stroke. Word-finding difficulty is the universal complaint in these patients.<sup>9</sup> Thus, understanding its cerebral basis, and whether it can be compensated for after left hemisphere damage, is of primary importance.

Conceptually driven word retrieval is enabled through lexical activation and selection. Lexical activation is the process by which a set of words is quickly activated through spreading activation from a corresponding set of features in semantic memory. Thus, when a speaker wants to say the word *dog*, semantic features such as *mammalian*, *domestic*, and *terrestrial* will be activated in semantic memory. Activation from these conceptual features will spread onto a set of words such as *cat*, *horse*, *rabbit*, and *dog*. Lexical selection is the process by which the intended word is then selected from this set (see Box 1 for a short perspective on the neurobiological underpinnings of the mental lexicon and associated notions of lexical activation and selection). Lexical activation and selection are usually thought to be dissociated processes, although lexical selection is possible only if lexical

<sup>a</sup>We note, however, that very early reports before the Common Era had already associated loss of speech with paralysis of the right side of the body (Hippocrates, *On Injuries of the Head*, in finger, 2000, p. 30).

<sup>b</sup>Interestingly, whereas Paul Broca was confident in linking the ability of articulated language to the third frontal convolution, he was more cautious in linking it to the left hemisphere in particular: “And, quite remarkably, in all these patients the lesion was on the left side. I don't dare to draw a conclusion from that and wait for new facts” (ibid. “Et, chose bien remarquable, chez tous ces malades la lesion existait du cote gauche. Je n'ose tirer de la une conclusion et j'attends de nouveaux faits”).<sup>3</sup> The left lateralization of this function was confirmed by Gustave Dax who reported 87 cases of right hemiplegia with loss of speech, 53 cases of left hemiplegia without loss of speech, and only 6 violating cases.<sup>4,5</sup>

activation has taken place.<sup>c,8,12,13, 14,15,16</sup> It has been proposed that these two sub-processes engage different brain regions: lexical activation has been associated with left temporal regions whereas lexical selection has been associated with left lateral and medial frontal regions.<sup>11,17</sup> Although word retrieval is traditionally thought to be supported by predominantly left-lateralized brain regions,<sup>18</sup> an increasing number of neuroimaging studies are also pointing to the presence of right-sided brain activity when engaged in tasks requiring word retrieval.<sup>18,19,20</sup> A key question concerns the nature of these right-sided brain activities in word retrieval: Are these activations merely epiphenomenal or do right-sided brain regions play a causal role in supporting word retrieval?

This question is of direct clinical relevance for individuals with left-sided stroke-induced aphasia. Determining which aspect of language production can or cannot be compensated for by their intact right hemisphere is crucial for these patients, as this information could potentially guide treatment options. In addition, assessing the effect of focal brain injury on specific cognitive functions remains the most reliable way to understand causality of human brain function<sup>d</sup>. Therefore, if specific aspects of language production cannot be compensated for after left hemisphere stroke, it can be taken as evidence that this component of language critically relies on the left hemisphere. We will review evidence supporting the idea that processes involved in word retrieval may be differentially compensated for after left hemisphere stroke-induced lesions and will suggest hypotheses as to why this could be the case.

There is debate as to the role of the right hemisphere in compensating for left hemisphere stroke-induced language impairment. Some researchers have argued for such a role,<sup>21,22,23,24,25</sup> while others have suggested that right hemisphere recruitment is sub-optimal in comparison to peri-lesional recruitment,<sup>26,27,28</sup> or even maladaptive to recovery of language functions.<sup>29,30,31,32</sup> However, results can be very different depending on the extent of the left hemisphere lesion,<sup>33</sup> and the relative involvement of the right hemisphere in language may be dependent on time post-stroke.<sup>34</sup> In addition, age of stroke onset has been shown to have a strong influence on functional outcomes in studies performed in adults,<sup>35</sup> and even more clearly in studies comparing children to adults.<sup>36</sup> In this review, we focus on studies performed in adults. Perhaps one of the most compelling pieces of evidence for the role of the right hemisphere in language in adults are the cases of left hemisphere stroke patients whose language is further impaired after a second right hemisphere stroke,<sup>21,25</sup> suggesting that not only is peri-lesional tissue involved in compensating for the degradation of language function after injury to the left hemisphere, but that right hemisphere brain regions may play a causal role as well. Evidence supporting this idea also comes from intracarotid amytal injections (i.e., WADA test) in which right-sided anesthesia was found to affect remaining expressive language abilities in patients with left-sided hemisphere injury.<sup>37,38</sup> This brief overview highlights that the right hemisphere may play a

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<sup>c</sup>We are aware that word retrieval and selection are considered to be synonymous in some psycholinguistic models and that other psycholinguistic studies have argued otherwise. Here, we refer to word retrieval as a more general term including both lexical activation and lexical selection, similar to Oppenheim *et al.*<sup>10</sup> and Piai *et al.*<sup>11</sup>

<sup>d</sup>Difficulties in word retrieval are also observed in other pathologies, such as the semantic variant of primary progressive aphasia or temporal lobe epilepsy. This review focuses on stroke patients because unilateral focal lesions are most informative with respect to the lateralization of brain function.

causal role in compensating for some language deficits after left hemisphere stroke. What remains unclear is which aspect of language, including word retrieval, can or cannot be supported by the right hemisphere. Indeed, language cannot be seen as one unitary function that is either intact or uniformly damaged; instead, it is a sum of sub-processes that rely on distinct underlying physiological functions (or factors).<sup>39</sup> We will argue that efforts to understand why word retrieval can or cannot be compensated for by the right hemisphere could benefit from focusing on the subprocesses that word retrieval relies on (for similar approaches in language in general, see Refs. 19 and 40).

While communication functions, such as prosody (but see Ref. 41),<sup>42,43,44,45</sup> pitch,<sup>46</sup> and certain aspects of discourse-level processing,<sup>47</sup> have been claimed to be right lateralized, this review will only focus on single word retrieval. First, we will focus on the left hemisphere regions supporting word retrieval and the consequences of stroke-induced lesions to these regions. Second, we will discuss the right hemisphere regions engaged in word retrieval and their potential role in compensating for disruption of word retrieval caused by left hemisphere lesions. In these sections, we will review results from both the functional imaging literature in healthy individuals and stroke patients and lesion-symptom mapping approaches in stroke patients. Finally, in our discussion, we will propose hypotheses as to why the different subprocesses of word retrieval can or cannot be compensated for by the right hemisphere.

## The role of the left hemisphere in word retrieval

### Left hemisphere regions associated with word retrieval in the healthy brain

As reviewed by Price,<sup>18</sup> many different left hemisphere regions of the frontal and temporal lobes have been associated with word retrieval in studies using functional magnetic resonance imaging (fMRI) and positron emission tomography (PET). These regions include posterior regions in the left middle and inferior temporal gyri (MTG and ITG),<sup>48,49,50,51,52,53,54</sup> and, more rarely, the superior temporal gyrus (STG)<sup>54,55</sup> and left hippocampus;<sup>55,56,57</sup> the left superior, middle, and inferior frontal gyri (MFG and IFG);<sup>56,58,59,60,61,62,63,64,65,66,67,68</sup> and medial frontal regions, such as the pre-supplementary motor area (pre-SMA)<sup>69,70,71</sup> and the anterior cingulate cortex (ACC).<sup>17,72,73</sup> Such a broad spread of participating regions implies that word retrieval has multiple components, or may even interact with other cognitive domains. To tease this out, many of these studies have relied on the idea that word retrieval is a competitive process.<sup>12,8,74</sup> Thus, when a speaker aims to say the word *apple*, not only will that word become activated,<sup>e</sup> but so will its semantically related neighbors (e.g., pear, orange, banana). These semantically related words interfere in the process of selecting the correct word, a notion that is supported by a category of speech errors referred to as semantic errors (e.g., “put the milk back in the oven”) and also by experimental findings.<sup>76,77,78,79,80</sup> For example, in the picture–word interference paradigm,<sup>76</sup> participants have to name pictures on which a distractor word is superimposed (Fig. 1). Performance is worse if the distractor word is from the same semantic category (e.g., picture of an apple with the distractor word *pear*; Fig. 1A) than

<sup>e</sup>Here, “activation” is to be understood in the sense of computational modeling, in which different words are represented as nodes or units that can have different activation values.<sup>75</sup>

when the distractor word is unrelated (e.g., picture of an apple with the distractor word *car*; Fig. 1B).<sup>11,17,48</sup> This effect is referred to as the semantic interference effect and is thought to reflect increased difficulty in word retrieval. Other paradigms eliciting semantic interference effects have been used in these studies,<sup>50,59,80</sup> as well as verb generation,<sup>53,58,63,64,65,72</sup> synonym/antonym generation,<sup>67</sup> verbal fluency,<sup>56,60,68,69</sup> simple picture-naming tasks,<sup>49,51,52</sup> and tasks comparing free versus constrained word generation.<sup>70,71,73</sup>

When task difficulty is increased, brain regions that help resolve this difficulty are predicted to show increases in functional activation. Such contrasts have suggested that frontal and temporal regions may be differentially involved in sub-processes of word retrieval, such as lexical activation and lexical selection. Schnur and colleagues<sup>59</sup> reported that the blood oxygen level-dependent (BOLD) signal in both the left IFG and left MTG was sensitive to semantic interference, using the blocked-cyclic picture-naming paradigm introduced by Kroll and Stewart<sup>78</sup> (Fig. 2). However, only activation in the left IFG positively correlated with the amount of errors made: participants with large left IFG activation in the semantically homogeneous condition (i.e., where there is more interference from semantically related alternatives; Fig. 2A) made more errors in this condition compared to the semantically heterogeneous condition (i.e., where there is less interference from semantically related alternatives; Fig. 2B). Such a correlation was not found for left MTG activation. The authors concluded that only the left IFG is necessary for the resolution of increased competition between semantically related alternatives in the paradigm they used, in agreement with what had already been suggested in verb generation tasks.<sup>58,81</sup> According to these studies, the left IFG would play a key role in lexical selection rather than lexical activation.

Piai and colleagues also compared left temporal versus frontal activity using the picture-word interference paradigm in both magnetoencephalography (MEG; using source localization)<sup>11</sup> and fMRI.<sup>17</sup> They found distinct responses to semantic interference in the following areas: activity in the superior frontal gyrus and ACC was larger for semantically related than for unrelated distractor words (they used the picture-word interference paradigm exemplified in Figure 1), whereas activity in the left temporal cortex, and more specifically, the anterior STG and posterior MTG and STG, was larger for unrelated than for related and identical distractor words (Fig. 3), in agreement with previous reports.<sup>82</sup> On the basis of these results, the authors suggested that the left superior frontal/ACC activity reflects selection among competing alternatives, whereas the left temporal activity reflects lexical activation. The reduced activity in the temporal cortex in response to related compared to unrelated distractor words (i.e., facilitation effect) would be because of the greater semantic distance between the picture name and the distractor when unrelated. This effect has been interpreted with respect to semantic priming, similar to what is observed in the speech comprehension literature.<sup>83</sup> Importantly, the use of a time-resolved technique, such as MEG, enabled the localization of the effects in a time window compatible with a role of these regions in word retrieval (between 350 and 650 ms after stimulus presentation), which is not possible with fMRI. Increased ACC activity for high versus low selection nouns was also reported in the verb generation task,<sup>72</sup> in agreement with a possible role for this region in lexical selection among competing alternatives. However, semantic interference effects have also been reported in the left temporal cortex (middle and posterior portions of

the left MTG or posterior STG) using the blocked-cyclic picture-naming paradigm.<sup>59,55</sup> Further investigation is needed to clarify which parts of the left temporal cortex are involved in lexical activation and selection, and at which point in time this occurs.

The role of the brain regions associated with word retrieval can also be dissociated on the basis of whether these regions have a more generic role, that is, whether they are also associated with other cognitive functions. Frontal regions in general have been associated with cognitive control processes in other domains and are not believed to be specifically associated with language<sup>84,85,86,87</sup> (although see Ref. 88). For example, Jonides and Nee have suggested the left IFG may be involved in resolving proactive interference between representations in working memory,<sup>87</sup> and Kan and Thompson-Schill suggested that this interference resolution process might be enabled through biased selection.<sup>85</sup> As reviewed by Ridderinkhof and colleagues,<sup>86,89</sup> the pre-SMA and ACC have been associated with response selection and monitoring outside of language. Thus, the increase in cognitive demands required for resolving semantic interference may call upon the domain-general cognitive control capacity of the frontal lobe. The distinction between domain specificity and generality is, however, less clear for left temporal regions.

This pattern of frontal versus posterior association with a specific cognitive process has been described more broadly by Fuster and colleagues (e.g., Refs. 90 and 91). Within the framework described by these authors, frontal brain regions, involved in execution, are linked to perceptual regions in the parietal, occipital, and temporal lobes to form “cognits,” which are different (although they can overlap partly) depending on the cognitive function involved. Thus, in the case of word retrieval, the posterior MTG and ITG could represent the perceptual component of the cognit, and the LIFG and pre-SMA/ACC could represent the executive component. The co-activation of these brain regions when retrieving words while speaking could be why it is sometimes difficult to dissociate the respective roles of these brain regions. The discussion in the next section, however, indicates that the deficits associated with damage to either of these brain regions do support this role distinction in the perception/action cycle.

### **Insights from stroke-induced aphasia on the causal role of left hemisphere cortical regions associated with word retrieval**

In this section, we first review studies using different methodologies to identify which brain regions may be critical for word retrieval in aphasic individuals, including lesion–symptom correlations and voxel-based lesion–symptom mapping (VLSM) in chronic stroke patients,<sup>92</sup> and reperfusion functional imaging in acute stroke patients. VLSM is a statistical voxel-by-voxel analysis that infers which brain regions are critical for task performance. Reperfusion imaging is typically based on diffusion-weighted imaging measures obtained immediately after stroke and after a few days post-stroke (e.g., 3–5 days in Ref. 93). Reperfusion of a given cortical area is defined as hypoperfusion at day 1 and normal perfusion at follow-up. This technique infers which brain region is critical in regaining specific abilities in the first days post-stroke by correlating improvement in task performance between the two times of testing with the reperfusion measures. Second, we review functional imaging studies in



chronic stroke patients that identify which brain regions may be involved in word retrieval recovery.

Even a cursory glance at the literature on aphasia will assert the importance of the left temporal lobe in word retrieval. Clinically, it is well known that aphasic persons with the most severe word retrieval deficits are those few patients with persisting Wernicke's aphasia, subsequent to left temporal lobe injury. These individuals make pervasive paraphasic errors in which target words are substituted with incorrect words, making their remarks difficult to understand. For example, in describing a man flying a kite, one man said, "They have there/ their young men, tree of the yellow that they use the marrows of the light of the wood." Such clear demonstrations of word retrieval deficits are also reflected in their poor object or picture-naming abilities, where target names are substituted with other words and/or jargon. Importantly, these individuals also fail on most comprehension tasks, even single word comprehension, and may not recognize the correct word even when it is given to them. Likewise, their picture-word or word-word matching performance is also compromised. However, the same patients easily demonstrate what the object is used for, never misuse such objects, and in most cases, carry on leading normal lives, except for their severe communication deficit. As described by Dronkers and colleagues,<sup>94</sup> it is the lexical representations that are lost in this patient group, or, the ties between lexical representations and their underlying concepts.

Traditionally, such word retrieval deficits have been associated with the left posterior superior temporal gyrus (Wernicke's area), but recent work has shown the importance of the left posterior middle temporal gyrus (pMTG) and underlying white matter in such a persisting disorder.<sup>94,95</sup> When large lesions occur in the pMTG and run deep into the fiber pathways that course beneath it, the effects of these lexical-semantic deficits are long lasting. In contrast, patients with posterior STG lesions tend to recover successfully within the first year post-onset of the disorder, though milder deficits may remain. Thus, the left pMTG is critical for lexical activation, as lesions here cause permanent impairments that do not resolve over time.<sup>f</sup> This evidence converges nicely with what has been suggested by the neuroimaging studies in healthy speakers.<sup>11,17</sup>

The relationship between the pMTG and lexical activation has been confirmed numerous times in subsequent studies using VLSM in larger numbers of patients. For example, Baldo and colleagues showed how stroke-induced lesions to the left pMTG are associated with persisting picture-naming difficulties.<sup>96</sup> The authors argue that this difficulty stems specifically from word retrieval deficits, as they used verbal fluency scores as a covariate to partial out brain regions associated with speech output processes and control for visual recognition deficits. This is the same brain region found to be associated with persisting comprehension deficits at the word level in the chronic stroke patients described above (Fig. 4).<sup>92,94</sup> As discussed below, patients with lesions restricted to the left prefrontal cortex (PFC), and especially the left IFG, do not have the same types of deficits.

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<sup>f</sup>Instances of such severe aphasia occur only very rarely in right hemisphere patients with crossed aphasia.



Reperfusion imaging in acute stroke patients has shown that both the left posterior MTG and inferior temporal/midfusiform gyri are critical for naming: reperfusion of these regions correlated with improved naming 3–5 days after initial scans.<sup>93</sup> This was also true for the posterior STG and left IFG but to a lesser degree. DeLeon *et al.* examined how deficits at different stages of speech production correlated with hypoperfusion in different cortical areas<sup>97</sup> and showed that hypoperfusion in the left posterior inferior temporal/midfusiform gyri correlated most strongly with impairment at the level of modality-independent lexical activation (i.e., the inability to name pictures in either the oral or written modality). The authors, however, did not differentiate lexical activation from lexical selection, and what they referred to as modality-independent lexical activation can be assimilated to word retrieval in our terminology. The importance of these regions for word retrieval has also been shown in patients with neurodegenerative diseases, such as in the semantic variant of primary progressive aphasia and semantic dementia, as well as epilepsy.<sup>98,99</sup>

Lesions in the left frontal lobes, and particularly in the inferior frontal gyrus, have also been associated with word finding difficulty.<sup>59,100,101,102</sup> Importantly, these deficits are not found with unilateral right PFC lesions (Fig. 5).<sup>101</sup> The deficits caused by left IFG lesions can be described as being of a different nature than those occurring after left temporal lobe lesions. Patients with lesions in the left IFG often know what they want to say but have trouble narrowing their search to the specific word. When given a choice between a few options or the onset of the target word, they can immediately identify the word they were looking for.<sup>g</sup>,<sup>104</sup> This differentiates them from patients with left MTG lesions, as shown by Schnur *et al.* who directly compared the performance of patients with left IFG lesions to that of patients with left MTG and STG gyri lesions in a task eliciting semantic interference (i.e., the blocked-cyclic picture-naming paradigm, in which pictures are repeated several times per block).<sup>102</sup> They showed that the semantic interference effect increased linearly across cycles, caused by increasing interference from semantically related alternatives in the homogeneous versus heterogeneous blocks, but only in patients with larger left IFG lesions. Thus, when a significant portion of the left IFG is damaged, overcoming the activation of semantically related words becomes progressively more difficult with the repetition of these semantically related neighbors. Patients with smaller left IFG lesions or left temporal lesions did not show this pattern. This, along with other evidence,<sup>59,100,101</sup> converges with the neuroimaging findings reported above for healthy speakers in suggesting that the left IFG is involved in overcoming interference caused by semantically related alternatives in the process of lexical selection. Left IFG lesions have been found to be associated with deficits in other processes, which has led several researchers to argue for a domain-general role of this brain region, in agreement with neuroimaging findings in healthy speakers. Thus, patients with left IFG lesions have been found to be impaired in the recent probes test that measures the ability to overcome proactive interference in working memory.<sup>105,106</sup> A number of researchers, including from our laboratory, have suggested that the left IFG plays a role in the anticipatory control of action.<sup>87,101,107</sup> Interestingly, recent results suggest that the left inferior frontal-occipital fasciculus (IFOF), which links the left IFG with posterior temporal

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<sup>g</sup>These symptoms are much more mild than those described by Paul Broca who associated the loss of articulated speech to lesions in the same region. However, as was shown later,<sup>103</sup> the lesions of the initial cases described also extensively involved the underlying insula and white matter, explaining the severity of the symptom.

regions, is engaged in both the resolution of semantic interference in picture naming and in working memory.<sup>108,109</sup> These conclusions again fit very well within the framework proposed by Fuster and colleagues,<sup>91</sup> where the perceptual component of the cognit (here, the posterior MTG/ITG) is critical for supporting the memory of words, whereas the executive component of the cognit (here, the left IFG) is critical for supporting the selection of these words for production. The coactivation of these brain regions and their interaction, possibly through the IFOF (or other temporal-frontal tracts, such as the arcuate fasciculus) would thus support efficient word retrieval in the healthy brain. Any injury to either part of this network is therefore expected to affect this cognitive function.

Several studies examining the brain correlates of recovery from stroke-induced aphasia have shown that the recruitment of peri-lesional tissue in the left hemisphere is positively correlated with recovery,<sup>26,27,28,110,111</sup> and this is also true for word retrieval.<sup>24,112</sup> Perani *et al.* reported functional neuroimaging findings in aphasic patients performing verbal fluency tasks.<sup>112</sup> These patients had lesions in different sites, but importantly, in the three patients with good recovery, the activation foci involved predominantly perilesional or undamaged regions of the language-dominant hemisphere. (One patient with crossed aphasia had a focus of activation in the right hemisphere.) Weiller *et al.* tested six recovered Wernicke's aphasia patients with lesions in the posterior parts of the left superior temporal gyrus, large parts of the left MTG and angular gyrus, and large parts of the posterior arcuate fasciculus.<sup>24</sup> These patients were PET scanned while performing verb generation and word repetition tasks. The most rostral portion of the IFG and middle part of the MFG were the only regions that showed more activation in the verb generation than in the word repetition task, and patients showed enhanced regional cerebral blood flow (rCBF) in these regions compared to controls. This argues for a role of the left frontal region in compensating for word retrieval deficits caused by lesions to the left posterior superior and middle temporal cortices. Alternatively, the increased frontal activation could reflect an increased effort in cognitive control to try to select words as a consequence of reduced lexical activation in the left temporal lobe. As we review below, these patients also showed rCBF increases in the right hemisphere.

Medial frontal regions, including the ACC and SFG, show increased activation in patients with word retrieval difficulties compared to controls,<sup>113</sup> and this is also the case for other language functions such as sentence comprehension<sup>34,114</sup> and word repetition.<sup>115</sup> Because these brain regions are involved in word selection and action monitoring processes outside of language,<sup>86,89</sup> Garenmayeh and colleagues have suggested that upregulation of activity in these regions following stroke can be explained by the fact that patients recovering from stroke-induced aphasia rely on domain-general processes in order to compensate for language deficits.<sup>40</sup> As discussed below, the same interpretation has been proposed for increased right frontal activity in these patients.

To summarize our discussion of the left hemisphere, abundant evidence demonstrates its role in supporting word retrieval. Aphasic individuals with deep left temporal lesions, particularly involving the pMTG, have the most severe lexical activation deficits that do not recover over time. Left lateral frontal patients also show retrieval deficits, but these deficits tend to be more in lexical selection with a different pattern of errors and larger semantic

interference effects. Individuals with right hemisphere injury do not demonstrate deficits in word retrieval, regardless of whether frontal or temporal lobes are involved, except in rare cases of crossed aphasia. Functional neuroimaging studies also show that left temporal, left lateral frontal, and medial frontal areas are associated with different aspects of word retrieval in healthy speakers. Here, the dissociation appears again: left temporal regions support lexical activation, while left frontal areas support lexical selection. The latter may relate to domain-general cognitive control mechanisms that affect other cognitive domains as well. Finally, functional neuroimaging in individuals recovering from left hemisphere-induced aphasia show predominantly perilesional activation but also activation in the lateral and medial PFC of the left hemisphere.

## The role of the right hemisphere in word retrieval

### Right hemisphere regions associated with word retrieval in the healthy brain

Although the right hemisphere has not typically been the focus of neuroimaging studies of word retrieval, many fMRI studies often report right hemisphere activation.<sup>55,59,65</sup> This right hemisphere activation is often smaller and less robust than left hemisphere activation. Right PFC activity has been shown to increase when word selection difficulty is increased.<sup>55,59,65,116,117</sup> For example, Buckner *et al.* compared two tasks,<sup>65</sup> stem completion versus verb generation, and found anterior right frontal activation (in the vicinity of the anterior MFG and IFG) only in the verb generation task, which requires more selection than the stem-completion task. In addition, it has been suggested that age-related increases in the activity of this region are due to increased difficulty in word retrieval in older relative to younger participants.<sup>118</sup> Right hemisphere activation modulated by word retrieval difficulty has also been reported for the temporal lobe. Schnur and colleagues reported BOLD activation in the right superior temporal gyrus that was sensitive to the difficulty of word retrieval.<sup>59</sup> Finally, using perfusion fMRI, both left and right hippocampi were found to be sensitive to the difficulty of word retrieval.<sup>55</sup>

According to a meta-analysis by Vigneau,<sup>19</sup> the participation of the right hemisphere in lexico-semantic processes, including word retrieval in language production, is low relative to the left hemisphere: 12 out of 34 contrasts looking at semantic associations (i.e., verb generation) were associated with bilateral activation, while 22 activated only left hemisphere regions. Only two clusters of right hemisphere activity associated with lexical-semantics were found in the right inferior frontal lobe. However, because these same clusters were found to be involved in other language processes (such as syntactic processing) and in tasks involving manipulation of verbal material in working memory, the authors argued for a non-specific involvement of these right frontal areas. This was also suggested by Basho *et al.*, who interpreted the activation observed in the right middle frontal gyrus and right anterior cingulate as being linked to sustained attention or working memory.<sup>117</sup> Thus, the right frontal activation found in language studies may not be specific to language, as also suggested by Geranmayeh and colleagues.<sup>40</sup> As mentioned earlier, the same suggestion has been made for the left frontal activation also found in tasks looking at proactive interference resolution in working memory.<sup>87</sup>

## Insights from stroke-induced aphasia on the role of right hemisphere cortical regions associated with word retrieval

We are not aware of studies reporting word retrieval deficits following unilateral right hemisphere stroke-induced lesions, except in cases of crossed aphasia.<sup>119</sup> This suggests right hemisphere regions do not generally play a causal role in word retrieval or that left hemisphere contributions are sufficient to assume any lost ability. However, a possible compensatory role of right hemisphere regions, and particularly right frontal regions, in recovery from left hemisphere stroke-induced word retrieval deficits has been proposed.<sup>h</sup>,<sup>22,24,104,112,122,123,124,125,126</sup>

Blasi *et al.* showed that the right frontal cortex may play a role in word retrieval learning in patients with left frontal lesions.<sup>22</sup> Specifically, the right frontal cortex was more activated in these patients than in controls in a word-stem completion task. Importantly, verbal learning evidenced by decreases in error rates and reaction times with the repetition of stimuli was accompanied by a decreased BOLD signal in the right IFG in patients with left frontal lesions but not in controls. In the controls, this pattern was observed in the left IFG and other regions. The patients with left frontal lesions were able to perform normally on a verbal learning task that typically engages the left frontal cortex, suggesting a compensatory role of the right IFG in verbal learning following left frontal infarct. The causal role of the right IFG in compensation for word retrieval deficits was tested by Winhuisen and colleagues,<sup>125</sup> using repetitive transcranial magnetic stimulation (rTMS) over the right IFG in aphasic patients with impaired verbal fluency, with the underlying assumption of creating transient dysfunction in this region. They reported a decrease in verbal fluency performance caused by rTMS to the right IFG in patients with limited perilesional recruitment determined from PET scans. This finding would argue for a role of the right IFG in compensating for deficits at the level of lexical selection. Conflicting rTMS results have also been reported, such that rTMS to the right IFG has facilitated aphasia recovery.<sup>30,31</sup> Differing results could be explained by the fact that Winhuisen *et al.* tested for right IFG activity (using PET) in addition to performing the rTMS study.<sup>125</sup> As suggested by Rijntjes *et al.*, providing information on the state of activation of right hemisphere regions pre-rTMS is critical in the interpretation of rTMS results.<sup>127</sup>

Although the right frontal cortex may be able to play a compensatory role in word retrieval following left hemisphere lesions, it does not appear to be able to completely replace the functions of the lesioned left frontal lobe. Perani *et al.* reported that patients with poor performance in semantic verbal fluency had extensive left and right dorsolateral prefrontal activation.<sup>112</sup> Patients who recovered well showed activation in left IFG, a similar pattern to controls. The bilateral involvement in patients with poor recovery was interpreted as reflecting increased “mental effort” in the task, compared to patients who had a functioning left IFG. Furthermore, Buckner *et al.* reported right frontal cortex recruitment, with a peak in the right inferior frontal cortex, in a word completion task in a patient with left frontal damage (tested 1 month post-onset).<sup>104</sup> This region was activated to a greater extent in this

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<sup>h</sup>Evidence for a compensatory role of the right temporal lobe, and particularly of the right posterior MTG and ITG, in word retrieval in language production has to our knowledge not been reported, even if a few studies have argued for a potential role of the right temporal lobe in recovery from left hemisphere stroke-induced lexical-semantic deficits in speech comprehension.<sup>120,121</sup>

patient compared to controls in the same task. This patient was, however, impaired in verb generation and other tasks involving generating more than the cued word. This suggests that the involvement of the right inferior frontal cortex was not able to completely overcome word retrieval deficits caused by the left frontal lesion. The authors suggest that this compensatory mechanism is unable to suppress more dominant responses while still allowing the selection of words under non-competitive conditions. The recruitment of right frontal areas in compensatory mechanisms for word retrieval deficits appears to depend on the extent of the left hemisphere lesion: in a study of two patients by Vitali *et al.*, only the patient with complete destruction of Broca's area showed an activation of the right homologous area post-training.<sup>122</sup> For the other patient, who had a smaller lesion partially sparing Broca's area, better performance was achieved post-treatment and was associated with left peri-lesional activation.

Finally, right frontal activation in word retrieval following left hemisphere stroke have been suggested to reflect more domain-general attentional recruitment, as has also been suggested in aphasia recovery in general<sup>40</sup> and in the studies performed in healthy speakers reviewed above. Weiller *et al.* found that patients with left temporal lesions had increased rCBF in right homologous areas (posterior STG, IFG, and MFG) compared to controls in both verb generation and word repetition, and also showed an additional area of activation in the right IFG that controls did not show.<sup>24</sup> The recruitment of the right IFG was related to intentional mechanisms or increased sustained attention for perception and comprehension of the stimulus nouns. Indeed, because this right inferior frontal activation was not stronger in verb generation than in word repetition, it was not interpreted as being involved specifically in word retrieval. Recruitment of right lateral and medial (pre-SMA) frontal regions in recovery from non-fluent aphasia can also be facilitated by certain types of aphasia therapies targeting nonspecific cognitive control processes. For example, Crosson *et al.* suggested that therapies focused on enhancing intention can increase the recruitment of these regions.<sup>123</sup> In addition, brain regions not typically associated with word retrieval may also be involved in recovery from word retrieval deficits in aphasia,<sup>126</sup> including the precuneus, right entorhinal cortex, thalamus, and left inferior parietal regions.<sup>110,111</sup>

To summarize this section, right hemisphere activation, albeit weak, has been observed during word retrieval in the healthy brain. In brain-injured patients, the right frontal cortex appears to play a role in compensatory processes following word retrieval deficits,<sup>22,125</sup> particularly for lexical selection deficits. Otherwise, right frontal recruitment following left hemisphere lesions is usually suboptimal compared to perilesional recruitment.<sup>104,112,122</sup> This is consistent with the findings reported in the broader literature on aphasia recovery, including in the case of syntactic processing.<sup>26,27,28,128</sup> Indeed, right frontal regions that are activated following left hemisphere stroke cannot completely overcome word retrieval deficits, presumably because these right frontal regions are predisposed for other functions.<sup>101,104</sup> This also seems to be the case when left focal injuries occur early in life, as tested in individuals who have sustained a pre- or perinatal left hemisphere stroke.<sup>129</sup> Indeed, even when the injury occurs early in life, the right hemisphere seems unable to fully accommodate language functions. Finally, some studies suggest that right frontal activation may reflect more domain-general attentional recruitment in both patients and controls and is not specifically associated with linguistic processes. Instead, right frontal activation seems to

be involved in cognitive control functions that have mostly been described in non-linguistic actions and that are eventually recruited when word retrieval is difficult. The precise role that these right frontal regions play to help compensate for language deficits after left hemisphere stroke needs to be specified in future studies. Indeed, different parts of the right frontal cortex have been associated with different cognitive control processes in actions in general (see Refs. 86 and 89 for reviews), but how and when they are involved when language functioning is damaged still needs to be investigated (however, see Ref. 130 for a possible role of the right IFG in linguistic response inhibition in healthy speakers).

## Discussion: hemispheric asymmetries in word retrieval

Consistent with known clinical findings, the left hemisphere has a higher potential for word retrieval compared to the right hemisphere. However, right hemisphere regions, and especially right inferior frontal regions, may engage in compensatory mechanisms following stroke to the left hemisphere regions associated with word retrieval. The potential of right hemisphere regions to help compensate for word retrieval deficits following left hemisphere stroke-induced aphasia appears to be different depending on the specific sub-process that is disrupted. Thus, right hemisphere regions and, in particular, right frontal regions appear to be better (although not optimal) at compensating for lexical selection than lexical activation deficits. As discussed earlier, this finding may reflect recruitment of more domain-general processes rather than linguistic ones.

### Why is there a left hemisphere bias for word retrieval?

As mentioned earlier, the enhanced role of the left compared to the right hemisphere for language in general has been known for over a century. Many studies have sought to understand the reasons for this left hemisphere bias. Here, we briefly review studies that hint at why word retrieval or the ability to link concepts to words is predominantly left lateralized.

In a series of experiments by De Renzi and colleagues on left hemisphere-lesioned patients that aimed to assess the ability of the left hemisphere in what was referred to as “associative thought,”<sup>131,132,133</sup> the authors were looking for non-verbal correlates of the ability to link different forms of an object to a unified concept (e.g., sound of a siren with the picture of its source, or picture of a clothed baby doll with an actual doll of a different form). Associative thought, as assessed by, for example, object-figure matching, was found to be more impaired after left rather than right hemisphere lesions.<sup>131</sup> In addition, Faglioni and colleagues found that performance on another test aimed to assess associative thought (i.e., sound-object matching test) was correlated with both the presence and the degree of aphasia: patients with greater language deficits performed worse.<sup>132</sup> More specifically, Saygin and colleagues tested for the domain specificity of the cortical regions involved in associative thought using a sound-object matching task closely matched with a word-picture matching task in stroke patients.<sup>134</sup> These authors found that similar cortical regions, including mainly the left posterior MTG and STG (i.e., Wernicke's area), contributed to performance in both tasks, using a VLSM analysis. It is thus tempting to think that this common brain substrate critical for amodal associative thought may be at the basis of the involvement of the pMTG in word



retrieval and especially lexical activation. Although associative thought is not linguistic in nature, it is of primary importance in language and particularly in word retrieval. A stronger capability of the left hemisphere for associative thought may thus underlie its stronger capability for word retrieval. However, it is difficult to draw a causal link between the two capabilities on the basis of these studies. Indeed, one could argue that the reason why associative thought is supported by left hemisphere regions is because it also supports language, especially in the case of the pMTG (see Saygin *et al.*<sup>134</sup> for a stronger association of the pSTG with the sound–picture matching task). This chicken-or-egg type of problem recurs often in searching for the cause of the stronger potentiality of the left hemisphere for language.

Studies on split-brain patients have shown that the difference between the left and right hemispheres may be more quantitative than qualitative, including at the level of lexical semantics: Gazzaniga and Hillyard suggested that the right hemisphere can attach noun labels to pictures and objects, only not as well as the left hemisphere (note, however, that only very few split-brain patients showed this ability).<sup>135</sup>

More recent research has tried to elucidate the basic physiological mechanism(s) underlying associative thought in auditory speech comprehension.<sup>1</sup> As suggested by Bornkessel-Schlesewsky and colleagues, dependency-based combinatorics may provide such a mechanism.<sup>136</sup> According to these authors and others,<sup>137</sup> cortical regions along the ventral stream are involved in identifying auditory objects from perceptual (e.g., phonemes) to conceptual units, and the most anterior portion of the temporal lobe is needed for accessing lexical semantics. This framework draws on the results of research performed in non-human primates in order to find common underlying principles of brain mechanisms involved in complex auditory processing. It provides a mechanistic explanation for the preponderant role of the anterior temporal lobe in lexical semantics as delineated by studies examining speech comprehension.<sup>138,139</sup> In addition, within this framework, the increased potentiality for lexical semantics of the left compared to the right hemisphere is naturally derived from the physiological asymmetries described for auditory regions (Box 2). Indeed, it makes sense that the regions involved in identifying concepts from complex auditory patterns would be closely linked anatomically to the regions able to detect fast acoustic changes (themselves needed to identify phonemes and syllables). Referring to other dual-stream models of speech perception (e.g., Ref. 140) allows us to link these superior and anterior temporal regions to the other temporal regions thought to be crucial for word retrieval, such as the posterior MTG and ITG. In this model, the pMTG and inferior temporal sulcus are considered as a lexical interface linking semantic to phonological information, which would be in agreement with the strong association that has been established between the pMTG and verbal knowledge in both speech comprehension and speech production tasks (see Ref. 141 for a meta-analysis). Such a framework, however, still needs to be developed for language

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<sup>1</sup>This type of approach was initiated by Luria who looked at linguistic processes as abstract functions being built upon more basic physiological mechanisms, which he termed *factors*.<sup>39</sup> Luria classified aphasic syndromes according to the specific brain factor that was disrupted. For example, a symptom such as kinetic apraxia, which is a deficit in the temporal organization of speech movements, is explained by the factor “disintegrated kinetic melody of movement,” which is caused by a lesion in inferior premotor areas (secondary motor cortex, BA 44 and 45).



production and represents a promising avenue to further the understanding of its neurobiological basis.

Hemispheric asymmetries are less clear concerning the size of the MTG and ITG in comparison with that of the planum temporale (see, for example, Ref. 142 and Box 2). However, studies on white matter as well as resting-state connectivity have revealed that the left MTG is connected through an extensive structural and functional connectivity pattern to other language regions.<sup>95</sup> A number of these tracts have been shown to be larger or more dense in the left than in the right hemisphere, including the arcuate fasciculus<sup>143,144</sup> and superior longitudinal fasciculus,<sup>145</sup> as well as more ventral pathways.<sup>144</sup>

Finally, heterogeneous results have been reported on hemispheric anatomical asymmetries of frontal regions associated with lexical semantics. Leftward asymmetry was found for the pars triangularis in 9 out of 10 patients with left-lateralized language as determined by Wada testing.<sup>146</sup> This, however, does not seem to be true for all frontal regions as assessed in healthy adults.<sup>142</sup> Similar to the MTG, the reasons for the asymmetric linguistic impact of left versus right PFC lesions may be found in the asymmetry of pathways connecting the left frontal lobe to left posterior language regions. Indeed, the abovementioned pathways connecting the MTG to frontal regions, such as the IFG, have been found to be larger or more dense in the left hemisphere.<sup>143,144,145,147</sup> It is not clear whether the anatomical asymmetries reported are a cause or a consequence of the specialization of the left hemisphere for language.

### **Domain generality and the two sub-processes involved in word retrieval**

As pointed out by neuroimaging studies in healthy and stroke patients and by the lesion–symptom correlation studies reviewed here, lexical activation and selection have been differentially associated with domain-general processes. Prefrontal regions found to be involved in lexical selection are also found to be involved in other cognitive processes. This is not clearly the case for regions associated with lexical activation. The domain-general aspect of prefrontal functions suggests that lexical selection processes should be more resistant to left hemisphere damage and should be better compensated for by right frontal regions than is lexical activation. Indeed, if lexical selection is enabled by brain regions that have a domain-general role, it may be easier for other brain regions in the right hemisphere to become involved if left hemisphere regions are lesioned, even if these right hemisphere regions are not as efficient in supporting the functions typically handled by the left hemisphere. In addition, we believe that a similar framework for understanding the role of the right hemisphere after left hemisphere stroke-induced language deficits may be applied to other components of language processing, such as at the sentence level, where multiple words have to be put together to form sentences.

Our hypothesis follows from the recent proposal by Geranmayeh and colleagues that domain-general networks play an important role in recovery from aphasia.<sup>40</sup> In their proposal, domain-general cortical regions play a role in language in challenging situations in healthy speakers. The same regions are also engaged in patients with aphasia, as these patients need to exert more cognitive effort to produce or comprehend language than do healthy speakers. A similar proposal has been made to explain the more prominent frontal

bilateral pattern of activity observed in older compared to younger adults when performing cognitively demanding tasks (i.e., the scaffolding theory of cognitive aging).<sup>148</sup> We argue that part of the brain regions associated with normal language production, such as the left IFG and pre-SMA/ACC, may also play a role in domain-general cognitive-control processes. When these regions are damaged—and therefore when the processes they support are affected—it may be easier for other regions involved in domain-general cognitive-control processes, such as those involving the right frontal lobe or other parts of the medial frontal cortex, to support recovery.

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**Box 1****Short perspective on the neurobiological underpinnings of the mental lexicon**

The concept of a mental lexicon and associated notions of lexical activation and selection stem from the field of psycholinguistics. There, words and how they are retrieved have been modeled in different ways, especially using neural network models (see Refs. 10 or 74 for examples of language production models). However, the neurobiological underpinning of these cognitive representations and how they are accessed remain to be investigated and constitutes a fascinating topic for future investigations. One promising direction is that of recent electrocortigraphic studies investigating the electrical oscillation patterns associated with different speech gestures, phonetic features, and words recorded directly at the cortical surface.<sup>149,150,151,152</sup> These linguistic units can be represented through distinct patterns of cortical oscillations (usually in the high gamma range: between 70 and 150 Hz) involving more or less extended regions of the human cortex. For example, Mesgarani *et al.* have shown that different populations of neurons in the superior temporal cortex (STG) are selective for different phonetic features and are hierarchically organized around acoustic cues (e.g., manner of articulation was found to be a stronger determinant for neuronal selectivity than place of articulation, which is also a less discriminant acoustic cue than manner of articulation).<sup>150</sup>

An extensive investigation of the cortical representations of words is less possible than with phonemes, given the exponential number of words in comparison to phonemes. Nevertheless, Pasley *et al.*<sup>152</sup> and Martin *et al.*<sup>153</sup> have shown that it is possible to decode the words that were heard or read (overtly and silently) by patients with relatively high accuracy by looking at cortical high-gamma activity, again predominantly recorded over the STG but also over the pre- and post-central gyri and higher-order cortical areas. These studies offer a rare window on the fine-grained spatiotemporal dynamics associated with linguistic properties and how they are represented in the brain. Similarly as for other percepts, the organization of the cortical representations of speech sounds seems hierarchical in that more simple acoustic features, such as tone, are represented in lower-level cortical areas, such as Heschl's gyrus,<sup>154</sup> and higher-order acoustic features, such as manner of articulation, are represented in higher-order cortical areas, such as the STG.<sup>150</sup> We can therefore imagine that for higher levels of abstraction, such as words or semantic categories, more extensive and associative regions will be involved, as has been shown, for example, in the visual domain.<sup>155</sup>

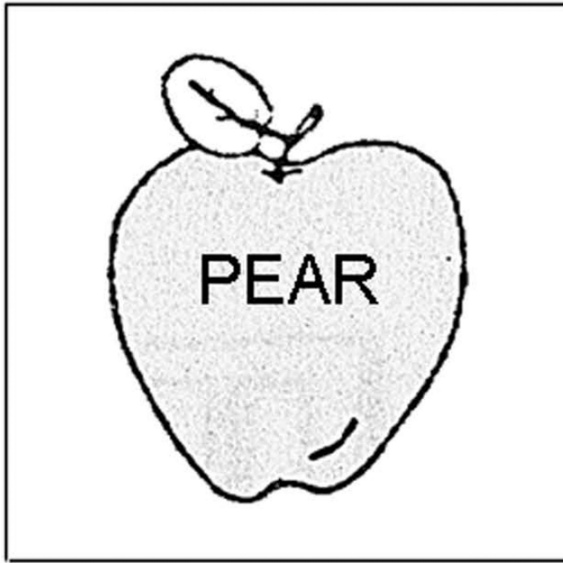
The study of the neurobiological underpinnings of word retrieval—including how the spread of activation takes place from concepts to words and how the correct word is then selected—is still unfolding. Interesting parallels may be made from studies looking at the neuronal basis of decision making, where biologically plausible models such as the drift-diffusion model have been implemented and tested with neuronal data, such as the firing rates of single neurons.<sup>156</sup> We note that evidence accumulation has recently been proposed to be a plausible model for the lexical selection process using naming latency

data.<sup>157</sup> Future studies will therefore need to investigate how such models may also serve to explain neuronal data associated with word retrieval.

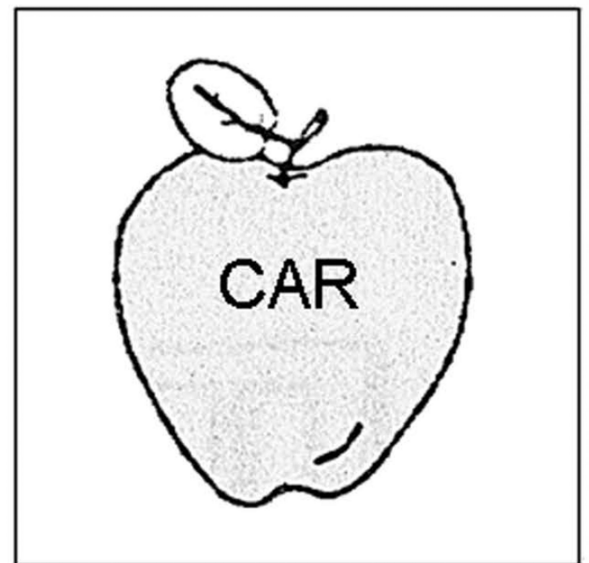
**Box 2****Hemispheric asymmetries of cortical auditory areas**

Asymmetries in human auditory areas (particularly in the planumtemporale) have been known since the 1960s.<sup>158</sup> In addition, left and right auditory areas have been shown to have unequal abilities in processing fast acoustic changes.<sup>159</sup> Research using dichotic listening experiments have suggested that fast acoustic changes are better perceived by the left than by the right hemisphere (Krashen in Ref. 160). In language, phonemes that differ only by the place of articulation are much harder to differentiate by the right than by the left hemisphere.<sup>161</sup> Place of articulation refers to where the obstruction occurs in the vocal tract. For example, /ba/ versus /da/ differ only in the place of articulation of the first phoneme, and /b/ is bilabial, whereas /d/ is apico-alveolar. Accordingly, cortical stimulation of the left STG has been shown to impair consonant discrimination, which relies on the ability to perceive fast acoustic changes, but not vowel discrimination, as vowels generally spread over a longer timeperiod.<sup>162</sup> Thus, temporal sequencing is better performed by the left than by the right hemisphere. This has been shown in linguistic and non-linguistic tasks, suggesting that this higher potential of the left compared to the right hemisphere in processing fast acoustic changes may be at the origin of the better ability of the left hemisphere in performing phonological processing (see also Giraud and Poeppel<sup>163</sup> for a neurobiological model based on asymmetrical left versus right hemisphere oscillation-based parsing). In agreement with this idea, patients with aphasia have (as a group) been shown to perform significantly worse than controls and right-brain-lesioned patients in nonlinguistic tasks requiring fine temporal order judgments,<sup>164,165,166</sup> although it is not clear which types of aphasic patients have these deficits. A recent review of detailed neuroanatomical investigations of the human brain's cytoarchitectonics hints as to why the left and right cerebral hemispheres could have different temporal sequencing abilities:<sup>167</sup> the way that cortical minicolumns are organized is different in the left compared to the right hemisphere. In the left hemisphere, cortical minicolumns are more widely spaced and have less overlapping dendritic fields, allowing for more independent minicolumn function. This type of organization has been suggested to be optimal for higher-resolution processing, in the sense of detailed feature analysis. In the right hemisphere, on the other hand, minicolumns are more densely packed, which has been associated with more overlapping, lower-resolution, holistic processing. Interestingly, genetic factors explaining hemispheric asymmetries have been found in the fetal brain.<sup>168</sup> In addition, axons of neurons in the superior posterior temporal lobe have been found to be more thickly myelinated in the left than in the right hemisphere, supporting faster processing speed in the left than in the right hemisphere.<sup>169</sup> These anatomical differences could very well explain the increased ability of the left hemisphere in identifying fast acoustic changes that are critical to our ability to perceive speech accurately.

## A. Related



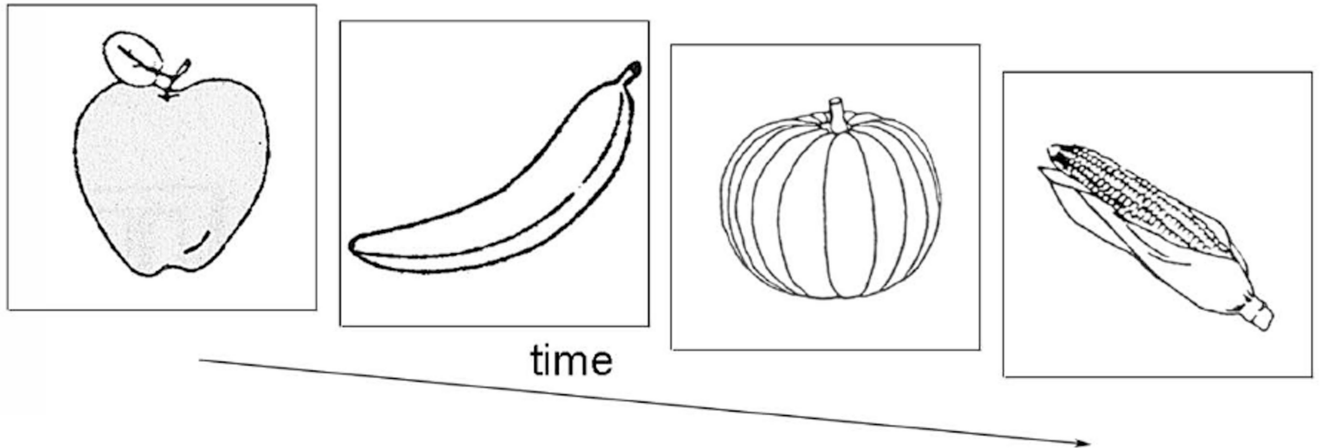
## B. Unrelated



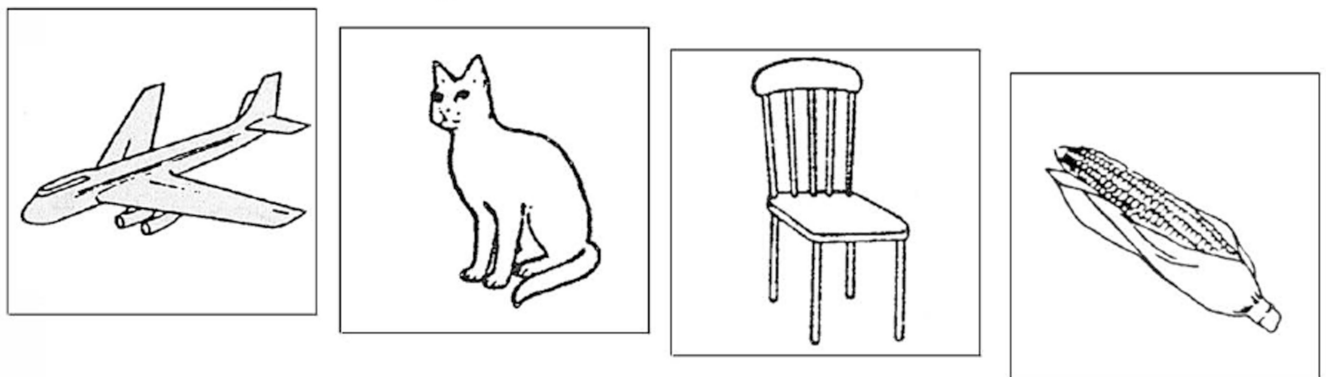
**Figure 1.**

Example stimuli for the picture–word interference paradigm. (A) Shown is a stimulus in which the distractor word is semantically related to the picture. (B) Shown is a stimulus in which the distractor word is semantically unrelated to the picture. Participants are instructed to name the picture as fast and as accurately as possible while ignoring the distractor word. Performance is typically worse for the type of stimuli shown in A than for the type of stimuli shown in B. This effect is referred to as the semantic interference effect.

### A. Semantically homogeneous block



### B. Semantically heterogeneous block

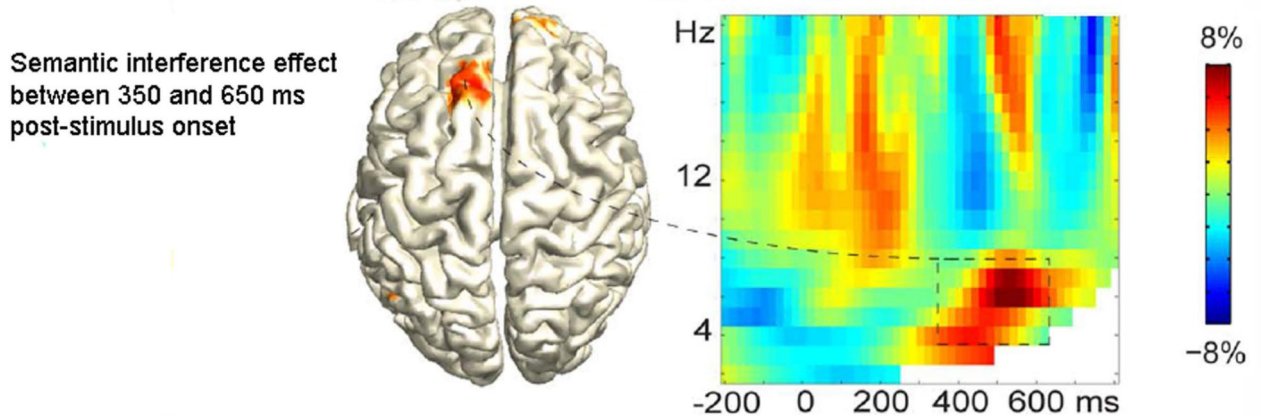


**Figure 2.**

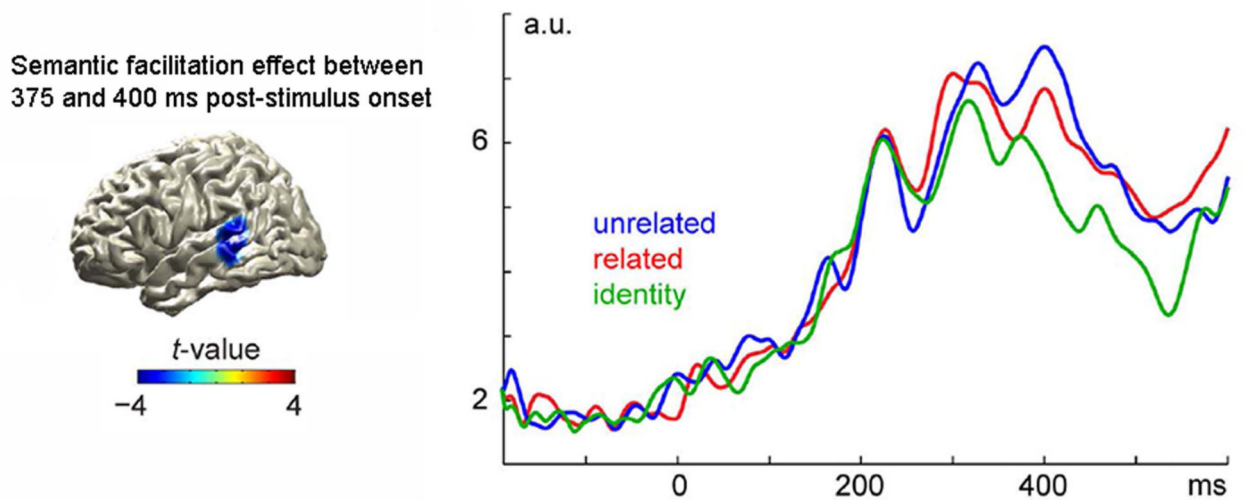
Example of stimuli used in the blocked-cyclic picture-naming paradigm in which pictures are presented either within semantically homogeneous (A) or heterogeneous (B) blocks. Pictures are repeated several times per block, usually five or six times. Participants are instructed to name the picture as fast and as accurately as possible. Performance is worse in homogeneous than in heterogeneous blocks. This effect is referred to as the semantic interference effect.



A. Semantic interference effect  
on the total time-frequency power localized in the left superior frontal gyrus



B. Semantic facilitation effect on the evoked  
brain response localized in the left superior and middle posterior temporal gyri



**Figure 3.**

(A) Shown on the left is the estimated source based on whole-brain analysis for the semantic interference effect (more activity for semantically related than for unrelated distractor words in the picture–word interference paradigm) for total time–frequency power (i.e., phase locked and non-phase locked). On the right, dashed rectangles in the time–frequency plot indicate the spectrotemporal cluster of interest (4–8 Hz, 350–650 ms after stimulus presentation). In this cluster, a relative power increase was observed in the left superior frontal source only. (B) Shown on the left is the estimated source based on whole-brain analysis for the semantic facilitation effect (more activity for semantically unrelated than for related distractor words in the picture–word interference paradigm) for evoked brain activity (i.e., phase locked) in the significant temporal cluster (between 375 and 400 ms post-stimulus). Shown on the right is activity of the left temporal cortex averaged over the

estimated sources for the different distractor types. Adapted, with permission, from Piai *et al.*<sup>11</sup>

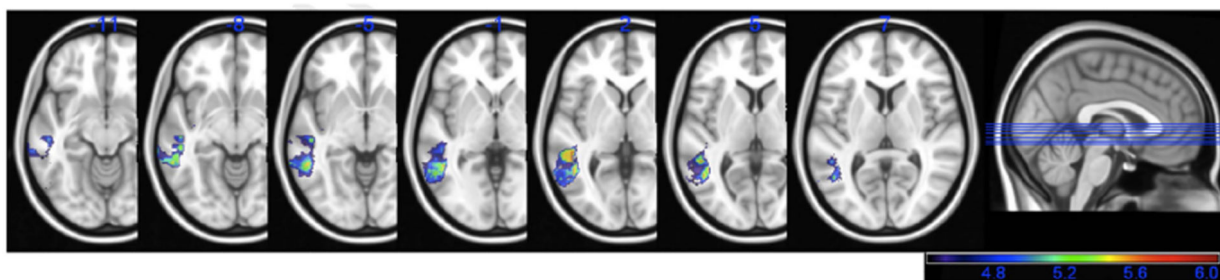
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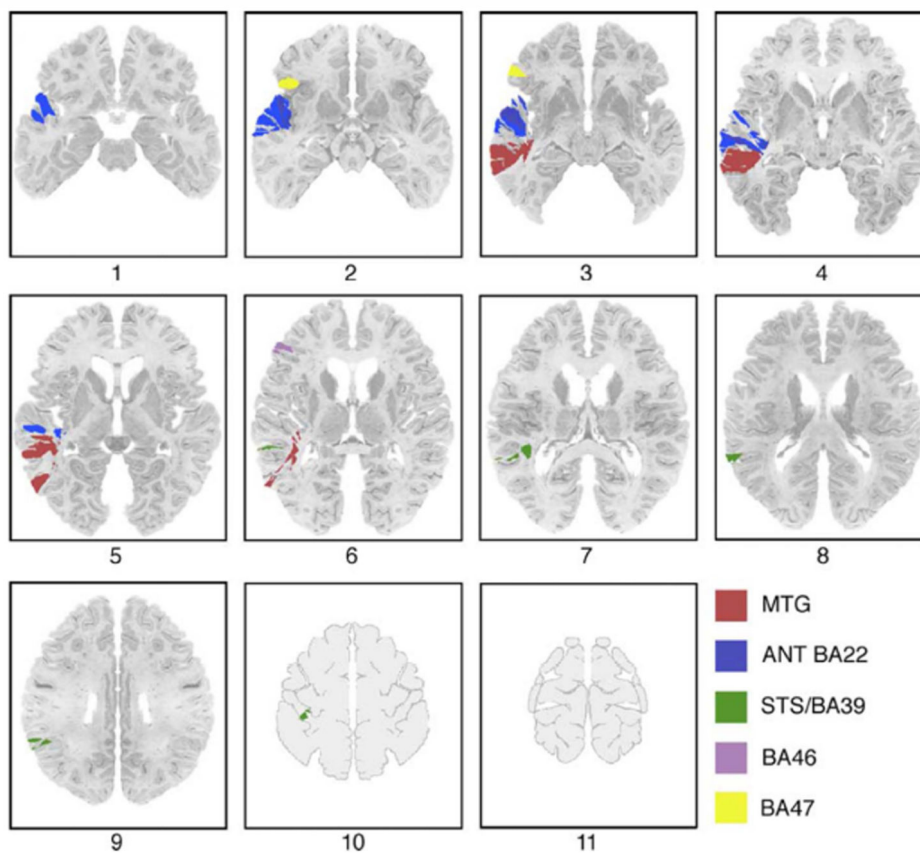
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A. Voxels associated with impaired word retrieval performance in speech production

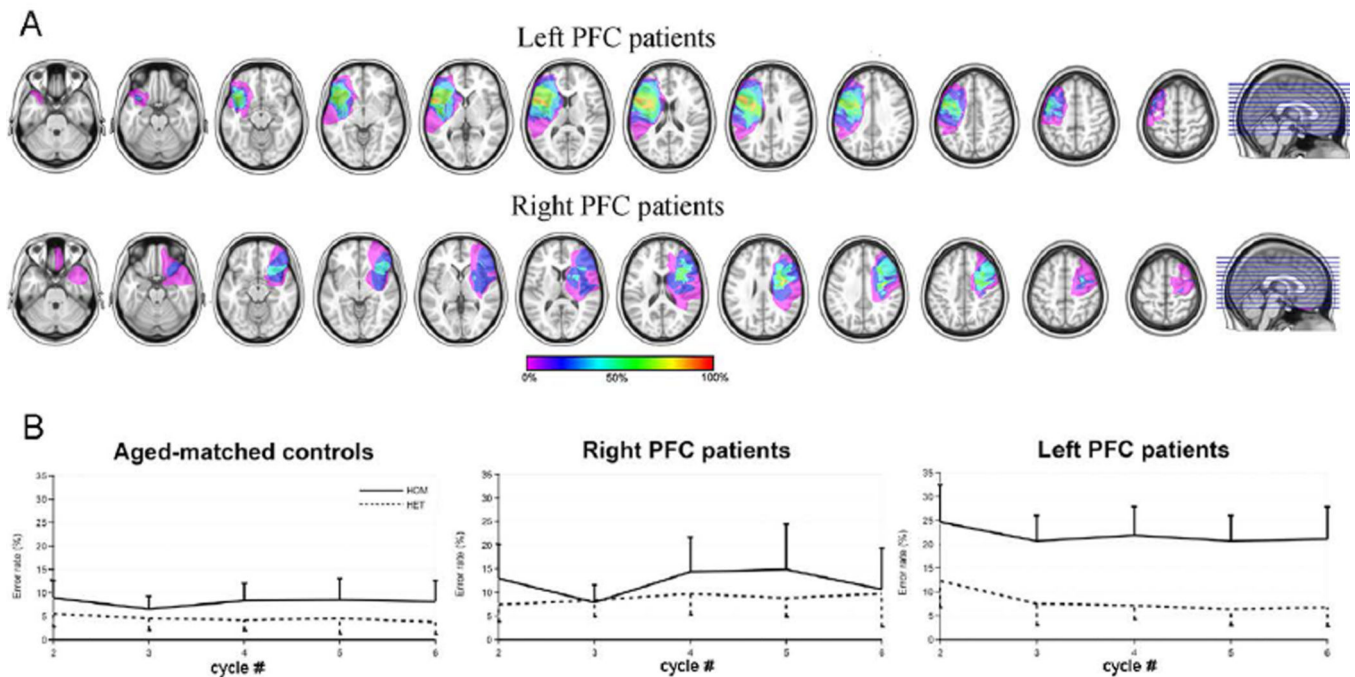


B. In red, VLSM-defined area found to be critical for single-word comprehension



**Figure 4.**

(A) Shown are significant voxels (as obtained from a VLSM analysis) associated with impaired picture-naming performance. Here, the effect of speech production deficits was covaried out. All voxels shown in color exceeded the critical threshold for significance, and the colors reflect increasing  $t$ -values from 4.43 to 6.06 (shown in purple to red). (B) In red, the VLSM area was found to be associated with single word comprehension deficits. Adapted, with permission, from Baldo *et al.*<sup>96</sup> and Dronkers *et al.*<sup>94</sup>



**Figure 5.**

(A) Lesion overlapping of the seven left (top) and six right (middle) PFC patients included in the analyses. Left PFC patients' lesions are centered in both the inferior frontal gyrus and the middle frontal gyrus. Right PFC patients' lesions are centered in the middle frontal gyrus. (B) Semantic context effect in a blocked-cyclic picture-naming task on error rates. Values for semantically homogeneous blocks (HOM) are depicted by the solid lines and values for the semantically heterogeneous blocks (HET) are depicted by the dotted lines. Mean values for cycles 2–6 are presented (in this paradigm, pictures are presented several times per block). Standard deviations are represented by the vertical lines (only positive values are presented for the homogeneous condition and only negative values are presented for the heterogeneous condition, for visual clarity). The semantic context effect (difference between homogeneous and heterogeneous blocks) is larger in left PFC patients than in right PFC patients and controls. Adapted, with permission, from Ries *et al.*<sup>101</sup>