Neurosci Bull April 1, 2015, 31(2): 220–226. http://www.neurosci.cn
DOI: 10.1007/s12264-014-1505-5

·Review·

What can atypical language hemispheric specialization tell us about cognitive functions?

Qing Cai[1], Lise Van der Haegen[2]

[1]Key Laboratory of Brain Functional Genomics, Ministry of Education, Shanghai Key Laboratory of Brain Functional Genomics, School of Psychology and Cognitive Science, East China Normal University, Shanghai 200062, China

[2]Department of Experimental Psychology, Faculty of Psychology and Educational Sciences, Ghent University, Belgium

Corresponding author: Qing Cai. E-mail: qcai@psy.ecnu.edu.cn

Recent studies have made substantial progress in understanding the interactions between cognitive functions, from language to cognitive control, attention, and memory. However, dissociating these functions has been hampered by the close proximity of regions involved, as in the case in the prefrontal and parietal cortex. In this article, we review a series of studies that investigated the relationship between language and other cognitive functions in an alternative way –– by examining their functional (co-)lateralization. We argue that research on the hemispheric lateralization of language and its link with handedness can offer an appropriate starting-point to shed light on the relationships between different functions. Besides functional interactions, anatomical asymmetries in non-human primates and those underlying language in humans can provide unique information about cortical organization. Finally, some open questions and criteria are raised for an ideal theoretical model of the cortex based on hemispheric specialization.

Keywords: functional lateralization; hemispheric specialization; language production; cognitive functions; co-lateralization

Introduction

Neuroimaging studies in the last years have defined many functionally-specialized brain regions. However, specialization alone cannot fully account for most aspects of brain function. Cognitive functions require the integration of distributed neuronal activity. One task may activate many cortical regions, and one region may be involved in many processes. For example, several important functions, such as attention, working memory, cognitive control, and language production, are critically dependent on the prefrontal cortex. Yet, anatomical architecture[1] and functional experience seem to create regularities in cortical organization across subjects. Functional ontologies can chart the complex relationship between anatomy and function by depicting which sub-process causes the activation of which precise anatomical region and *vice versa*[2], provided that both anatomical networks and task contexts are dynamic. Recently, a many-to-many approach was presented because functions not only seem to be rooted in distributed networks, but configured circuits also interact with each other[3]. Some recent studies have modeled the brain as graphs consisting of different functional networks, and these studies converged on a set of fundamental attributes of human brain organization, in line with those found in nonhuman primates[4,5]. We argue that the way the cortex is organized (be it according to a one-to-one, one-to-many, or many-to-many mapping between anatomy and function) can be uniquely investigated by looking at the anatomical and functional correlates of (a)typical lateralization of language. It is well-documented how behavioral tasks and handedness can help identify subjects with (a)typical speech dominance, and there is a rich neuroimaging literature on the sub-processes of language. Moreover, language seems to be the most pronounced lateralized function so far. In this review, we further discuss studies that have used (a)typical speech dominance to explore the organization of other language-related and non-language functions. Subjects with atypical lateralization allow investigation of what consequences a shift in one function has for other networks that do not seem to be related at first sight. As such, anatomical and functional relationships that are otherwise difficult to dissociate can be mapped in a healthy population.

Functional Lateralization of Language and Handedness

The capacity for language is unique to human beings. Its well-documented lateralization makes it an even more intriguing function. Left hemisphere (LH) dominance for language production is a robust finding at the population level. In the 19th century, Marc Dax and Paul Broca first reported that speech problems are more likely to occur after injuries to the frontal part of the left hemisphere than after injuries to the right hemisphere (RH). Some early evidence for language dominance came from split-brain patients, whose corpus callosum was sectioned to control intractable epilepsy. The seizures were decreased by disconnecting the two hemispheres. Testing of each disconnected hemisphere in split-brain patients seems to show quite extensive language understanding in the isolated RH, but no speech output[6]. These results therefore suggest the dominant role of the LH in language production, and this hemispheric specialization has been supported by a wealth of evidence from neuroimaging studies in the last two decades, for the great majority of individuals.

Similar to the population-level bias towards LH dominance for language, a strong bias towards the right hand at the population level has probably existed for more than ten thousand years[7]. A popular way to define handedness is using questionnaires such as the Edinburgh Handedness Inventory[8] or the Waterloo Handedness Questionnaire[9], or a finger-tapping test[10]. In such questionnaires, a handedness index is calculated based on the self-reported handedness in a list of common manual tasks. However, the nature of handedness is so far unclear. An influential genetic model proposed by McManus[11] suggests that hand preference is controlled by an allele, which can be either right-biased (the D variant) or not biased (the C variant). Individuals with DD alleles are assumed to be right-handed; the handedness of individuals with CC alleles is random; and those with DC alleles have a 75% chance of right-handedness. A good fit of the data is obtained when the proportion of the C variant in the population is estimated to be around 0.155. However, although a few candidate genes have been proposed, and recent twin studies have confirmed a significant genetic influence on handedness, the genetic effects are complex and small, which suggests a polygenic control of handedness rather than a single-gene model[12].

The relationship between cerebral lateralization of language and handedness has been studied for years, and the link seems to be weak and indirect. On the other hand, left-handers are excluded from most cognitive studies in order to reduce variance in the data. Recently, a few studies suggested a weak but clear relationship between these two lateralized functions at the population level. For example, Knecht *et al.*[13] found that the likelihood of RH language dominance as measured with a word-generation task increases with the degree of left-handedness: ~1–5% of right-handed individuals are right-lateralized for language, and so are ~10–25% of left-handers. Given that LH language dominance cannot be generalized to the whole population, cognitive studies should take into account both left-handed and right-handed subjects[14]. Not only looking at typically organized cortices but also investigating atypical lateralization can help to unravel cortical organization. A shift in the hemispheric specialization of one functional network can reveal how another network is associated with or dissociated from the first. Language might be an interesting first network to look at, because RH speech dominance is rare but can be found in healthy people, especially in left-handed individuals, and this inspired the series of studies outlined below.

Is Language Dominance Related to Other Cognitive Functions?

Based on the report by Knecht *et al.*[13], Van der Haegen *et al.*[15] carried out large-scale screening of 265 left-handers and determined their language dominance. The left-handers first took part in a behavioral visual half-field experiment, and were classified as atypical RH- or typical LH-dominant for speech if they were fastest at naming pictures and words presented on the left or right half of the screen, respectively (because of the partial crossing of optic fibers visual information is sent to the contralateral hemisphere). Their speech lateralization was confirmed in an fMRI word-generation task, in which activity in the inferior frontal gyrus was compared between the left and right hemispheres.

Then the left and right speech-dominant subjects took part in a study on reading lateralization. This made it possible to determine whether reading is dominantly processed in the LH because of low-level processes such as visual spatial frequencies[16,17] or because language sub-processes co-lateralize in order to optimize the integration of visual and phonological information. The lateralization indices based on activity in the ventral occipito-temporal (vOT – also termed the visual word form area[18] as it responds to (pseudo)words invariantly of retinal location, case, or font) during lexical decision showed that right dominance for speech in frontal language regions is most often accompanied by right lateralization of word recognition[19,20]. These results thus lend strong support to the hypothesis that vOT activity in word reading is adjusted 'top-down' by anterior language structures, instead of being automatically activated in a 'bottom-up' way. In other words, the vOT visual word recognition system is primarily a language system and not a visual processing system.

Although (a)typical functional lateralization can provide information on how language sub-processes interact, language does not exist in isolation from other cognitive functions such as memory and attention. For instance, a network has been shown to respond to different kinds of cognitive challenges[21]. This network, sometimes referred to as the 'cognitive control network' or 'multi-demand system', involves a set of regions in the prefrontal and parietal cortex, including dorsolateral prefrontal regions (cortex in and around the posterior part of the inferior frontal sulcus), anterior insular and adjacent frontal operculum, pre-supplementary motor area and adjacent dorsal anterior cingulate cortex, and regions in and around the intraparietal sulcus. Recent studies have investigated whether and how this domain-general cognitive control network is engaged in language processing, and have shown that cognitive control plays an important role in language, at least in language production (e.g. using a missing-letter paradigm[22] or verbal fluency[23]). In contrast, other studies (e.g. using a sentence understanding task[24]) found little or no response in language regions to non-language cognitive control. However, given that the regions involved in these functions are located in close proximity, especially in the prefrontal cortex, it is not easy to clearly separate them and draw conclusions. Again, this issue can be investigated *via* functional lateralization as an alternative approach. The research group that identified the (a)typical speech-dominant group noted above also examined the relationship between language production and non-language cognitive control, and found that cognitive control in a non-language task-switching paradigm is highly co-lateralized to the dominant hemisphere for language production (Fig. 1B, Cai *et al.*, unpublished data), which might indicate that the two functions share mechanisms. Apart from language production, visuospatial attention is the most salient lateralized cerebral function. Complementary specialization of language and visuospatial attention has been observed in the majority of the population. Does this complementary specialization have a causal origin (the lateralization of one function causes the opposite lateralization of the other for best parallel performance, as proposed by Kosslyn[25]), or is it rather a statistical phenomenon (different functions lateralize independently)? By testing the two groups of left-handers with opposite hemispheric dominance, Cai *et al.*[26] reported that right dominance of language is always accompanied by an atypical left-lateralized fronto-parietal network underlying visuospatial processing during a landmark task, both at the group and at the individual levels (Fig. 1A). These results clearly support the 'causal origin' hypothesis of complementary specialization, and we could speculate that this crossed lateralization has a longstanding evolutionary origin.

Furthermore, it has been reported that language and praxis (i.e., tool use) networks are highly overlapping and co-lateralize to the dominant hemisphere for language. This overlapping network involves the dorsolateral prefrontal cortex, posterior parietal cortex, supplementary motor area, and dorsal and ventral premotor cortex[27] (Fig. 1C).

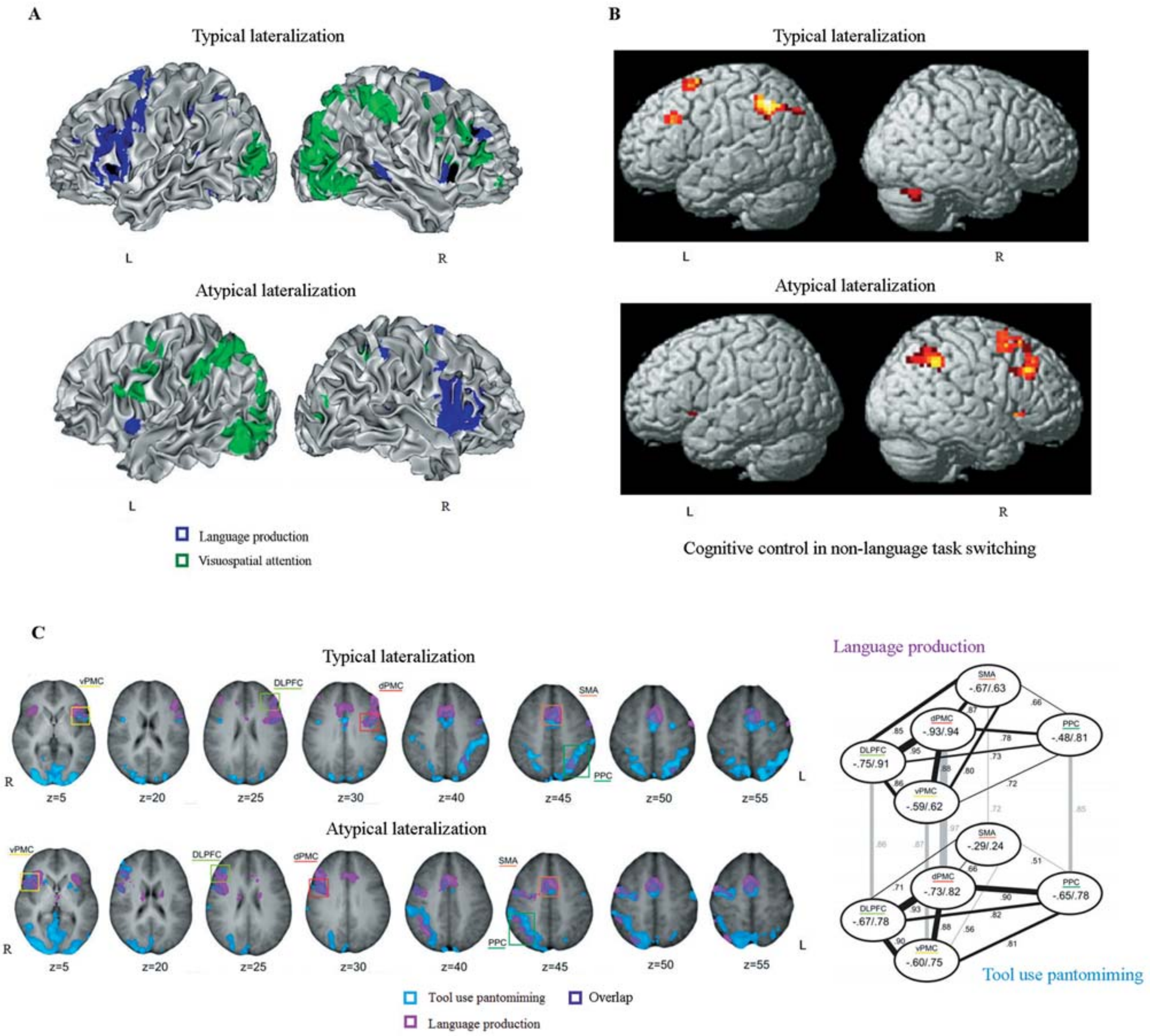

Fig. 1. **(A) Language production and visuospatial attention lateralize to different hemispheres, independent of the side of lateralization; overlapping activations for the two tasks only occur in the insula and the supplementary motor area (SMA). (B) Cognitive control in a non-language task-switching paradigm is lateralized to the dominant hemisphere for language production, independent of the side. (C) Left panel: Language production and tool-use pantomiming co-lateralize to the same hemisphere, with overlapping activations (depicted in purple marked out by squares) in dorsolateral prefrontal cortex (DLPFC), dorsal premotor cortex (dPMC), ventral premotor cortex (vPMC), posterior parietal cortex (PPC) and SMA. Right panel: Co-lateralization within and between paradigms. The lateralization index (LI) of each region is listed inside the ellipses (typical/atypical lateralization group); black and gray connecting lines represent significant correlations between the LIs of the regions within and between paradigms, correspondingly. Note that these studies were conducted in left-handers. The figure is reproduced from Cai *et al.*, Proc Natl Acad Sci U S A 2013[26] and Vingerhoets *et al.*, Cortex 2013[27].**

Both the direction and degree of lateralization during word generation correlate with the lateralization pattern during tool-use pantomiming. Most participants were left-handed, but the same pattern was found in one right-handed and one ambidextrous person. This indicates that handedness can only serve as an indirect selection criterion for models linking gestures and speech to explain the evolution of human language[28]. Rather, the functional asymmetry of language or tool use can give new insights in this domain.

To conclude, functional lateralization studies seem to offer a different approach to investigate the relationship between different functions. Co-lateralization of different cognitive functions, or the dependency of their functional lateralization (i.e. complementary specialization), may suggest an interaction between the functions of interest, either online or during evolution/development. These studies could therefore add more evidence to our current research from a different point of view.

It should be noted, however, that these studies have so far been limited to pre-selected left-handers. Therefore, further studies are expected to confirm whether this conclusion can be generalized to the whole population, including both left- and right-handers. We should also note that many tasks widely used in current studies are not defined precisely enough, in the sense that they often involve cognitive functions other than the one of interest, such as memory retrieval, attention, and decision-making. Besides, a cognitive functional system, no matter which one, should not be considered as a whole, but rather a set of primitives (i.e. a ‘parts list’ of representational elements, as well as a list of elementary functions, from both the cognitive side and the neuroscience side[29]). Knowing how distinct parts of a cognitive function co-lateralize within an individual offers much richer and more detailed information about the mechanism underlying this cognitive function.

Asymmetries in the Human Brain and in Our Primate Relatives

Although the hemispheric lateralization of language is a specific cortical feature of the human brain, it is now clear that asymmetries of brain and behavior exist not only in humans but also in vertebrates and invertebrates[30-33]. Some of the asymmetries in animals parallel those in humans, probably serving as evolutionary precursors. It would therefore be unjust to argue that functional (language) lateralization studies in humans are the single best way to investigate cortical organization. Unique information for brain research can also be obtained by linking functional lateralization to the anatomical structure it is based in and by looking at the evolution of functions.

Chimpanzees, our closest relatives, show both a bias towards right-handedness at the population-level[30] and brain structural asymmetries in regions homologous with human language-relevant regions[31]. Furthermore, the direction of hand preference for clapping explains a significant portion of the variability in asymmetries of the planum temporale and inferior frontal gyrus[30]. In contrast, no significant population-level cerebral structural asymmetries have been reported in the macaque, except for the surface area of the superior temporal sulcus[31]. The asymmetries in chimpanzees are therefore suspected to be a precursor of human language lateralization.

A recent work by Leroy *et al.*[34] pointed out a robust human-unique asymmetry in the depth of the superior temporal sulcus (STS), which is deeper in the right than the left hemisphere. This asymmetry is systematically present in humans at all ages, but hardly detectable in chimpanzees and absent in macaques. Given that the STS region plays a crucial role in human linguistic functions, this asymmetry is suspected to be the spot underlying language lateralization. Nevertheless, the same study compared individuals with LH dominance for language and those with RH dominance, and found no significant difference in STS asymmetry between the two groups — they both showed a deeper STS on the right side. That is, this human-unique asymmetry seems not to be correlated with the functional lateralization of language. The morphometric results from the same two populations also showed that functional lateralization is only subtly linked to anatomical asymmetry, with differences in the surface area of the insula, part of the planum temporale, and the vOT[35]. Similarly, a leftward asymmetry in the relative fiber density of the arcuate fasciculus – connecting frontal and temporo-parietal language areas – was found for left- and right-handers irrespective of their functional lateralization during verb generation[36]. One study recently did find a relationship between the gyrification pattern of Heschl’s gyrus involved in primary auditory processing and functional asymmetries during word listening, again irrespective of handedness[37]. To conclude, only subtle anatomical asymmetries have been linked so far to clear (a)typical functional language lateralization (note that other studies did relate the degree of only leftward lateralization to anatomical variations, e.g. [38]).

Towards an Ideal Theory of Hemispheric Specialization for Different Functions

Studies on functional lateralization in recent years have already shed light on the relationship between different cognitive functions. Nevertheless, the nature of hemispheric specialization is still far from clear.

For further research, an ideal theory of cerebral functional lateralization is expected to fulfill these requirements: (1) to include as many lateralized modules/functions as possible and take into account their co-lateralization; (2) to amplify research on the lateralization of functions other than speech so that they can serve as a starting point for lateralization research (i.e. comparing lateralization of sub-processes to the main function, charting the prevalence of (a)typical lateralization, and creating behavioral screening tasks to identify (a)typical subjects); (3) to better define distinctive (sub-)function systems involved in different cognitive functions, both theoretically and computationally, so that overlapping brain regions and networks can be optimally interpreted; (4) to clarify the link between functional lateralization and anatomical asymmetries including morphometric asymmetries and asymmetries in fiber pathways; (5) to take into account both left-handed and right-handed populations to be able to explain the probability and mechanism of atypical lateralization and handedness in some individuals; and (6) to associate the human model with human diseases, animal models, and genetic models.

Received date: 2014-06-08; Accepted date: 2014-11-28

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