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Neuroimaging of Language: Why Hasn't a Clearer Picture Emerged?

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Abstract

Two broad questions have driven dozens of studies on the neural basis of language published in the last several decades: (i) Are distinct cortical regions engaged in different aspects of language? (ii) Are regions engaged in language processing specific to the domain of language? Neuroimaging has not yet provided clear answers to either question. In this paper, we discuss one factor that is a likely contributor to the unclear state of affairs in the neurocognition of language, and that, in our opinion, has not received sufficient attention in the recent literature. In particular, fMRI studies of language have relied, almost exclusively, on group analyses, in which data from multiple individuals are co-registered to and analyzed in a common space. We argue that this approach can obscure functional specificity because of the anatomical variability across individual brains, and we advocate the use of an alternative approach – the functional localization approach – that circumvents this problem.

Introduction

Two broad questions have driven dozens of studies on the neural basis of language published in the last several decades: (i) Are distinct cortical regions engaged in different aspects of language? (ii) Are regions engaged in language processing specific to the domain of language? Whereas neuroimaging has provided some valuable insights into the functional organization of the language system in the brain, these questions have not yet been answered definitively. Instead, much of what we know still comes from cases of selective brain damage. This situation contrasts strikingly with some other cognitive domains: for example, neuroimaging has provided a much more detailed picture of the brain basis of high-level visual processing than had emerged from patient data (see Kanwisher 2003, for a review). In this paper, we discuss one factor that is a likely contributor to the unclear state of affairs in the neurocognition of language, and that, in our opinion, has not received sufficient attention in the recent literature. In particular, functional magnetic resonance imaging (fMRI) studies of language have relied, almost exclusively, on group analyses, in which data from multiple individuals are co-registered to and analyzed in a common space. We argue

that this approach can obscure functional specificity because of the anatomical variability across individual brains, and we advocate the use of an alternative approach that circumvents this problem.

We start by briefly synopsizing the current state of the neuroimaging of language literature.[1] We then review the literature demonstrating high anatomical variability across individuals, especially in the higher association cortices. We proceed to summarize some data from the clinical literature where the individual-subjects fMRI approach has been used in the last several years to guide preoperative electrocortical stimulation mapping. These studies demonstrate substantial functional variability (differences in the location and size of language-sensitive regions) across individuals, which (i) is expected given the high levels of anatomical variability, and (ii) highlights the problem of inter-subject averaging of functional data. However, these studies also demonstrate the feasibility of localizing language-sensitive regions in individual subjects, given the robustness of activations for language tasks. Consequently, we advocate the use of the individual-subjects functional localization approach, which involves identifying a region or a set of regions engaged in the cognitive process of interest, and subsequently investigating the functional profiles of the regions so identified (Saxe et al. 2006; c.f. Friston et al. 2006).

The Neural Basis of Language: Where Things Stand

In 1874, the German neurologist Carl Wernicke advanced a proposal concerning the functional architecture of the language system. Based on his own research and that of the French physician Paul Broca, he hypothesized that a left frontal region (Broca's area) is critically involved in the production of speech. The proximity of this region to the motor cortex, and in particular, to the regions of the motor cortex responsible for controlling the muscles of the face, mouth and vocal cords, appeared consistent with this idea. He further hypothesized that a left temporal region (Wernicke's area) is critically involved in the perception of speech. The proximity of this region to the auditory cortices appeared consistent with this idea (see e.g., Geschwind 1970, for more details on Wernicke's original proposal). Whereas these hypotheses provided a good starting point for investigating the neural basis of language, they turned out to be wrong in several respects.

First, data from patients with brain damage have revealed that (i) lesions in and around Broca's area do not always lead to deficits in language production, and lesions in and around Wernicke's area do not always lead to deficits in language comprehension; and (ii) deficits in language production/comprehension are sometimes observed without the accompanying lesions in Broca's/Wernicke's areas (e.g., Mohr 1976; Mohr et al. 1978; Naeser and Hayward 1978; Alexander et al. 1990; Willmes and Poeck 1993; Caplan et al. 1996; Dronkers 1996, 2000; Caplan et al.

2007). Thus, Broca's area is neither necessary nor sufficient for language production. And similarly, Wernicke's area is neither necessary nor sufficient for language comprehension.

Second, neuroimaging data have revealed activations in left frontal regions for a wide variety of language tasks (many of these not related to language production (e.g., Stromswold et al. 1996; Dapretto and Bookheimer 1999; Ben-Shahar et al. 2003)), as well as for tasks in other cognitive domains (e.g., Paulesu et al. 1993; Braver et al. 1997; Gabrieli et al. 1998; Binkofski et al. 2000; Duncan and Owen 2000; Fincham et al. 2002; Hamzei et al. 2003; Levitin and Menon 2003; Buccino et al. 2004; Nishitani et al. 2005; Koechlin and Jubault 2006; Tettamanti and Weniger 2006; Novais-Santos et al. 2007). Similarly, activations observed in left temporal/temporo-parietal regions have not been restricted to language comprehension tasks or even to the domain of language (e.g., Bischoff-Grethe et al. 2000; Saxe and Kanwisher 2003; Nakai et al. 2005). Thus, Broca's area doesn't appear to be specific to language production. And similarly, Wernicke's area doesn't appear to be specific to language comprehension.

And finally, other regions outside of the left frontal/temporal regions have been observed in neuroimaging studies of language, including the right frontal/temporal regions, regions in the parietal and even occipital lobes, the cerebellum, and some subcortical structures, such as the basal ganglia and the thalamus (e.g., Desmond and Fiez 1998; Murdoch 2001; Frisch et al. 2003; Booth et al. 2007; Timmann and Daum 2007; Dikker et al. 2009). Thus, language appears to rely on a network much more extensive than the initially hypothesized set of two primary regions in the left frontal and left temporal lobes.

Whereas some convergence has transpired across studies and laboratories with regard to the relationship between some aspects of language and particular brain regions,[2] many open questions remain about the functional specificity of these regions. As an illustration of the current state of affairs, consider Figure 1, which summarizes the results of Vigneau et al.'s (2006) meta-analysis of 730 activation peaks (coming from 129 reports) for three types of language tasks: phonological tasks (marked in blue), semantic tasks (marked in red), and syntactic tasks (marked in green). The upper panel shows the distribution of all the activation peaks, and the lower panel shows the results of a cluster analysis, which revealed 30 peaks across the frontal, temporal, and parietal lobes. As can be seen from either panel, there is substantial overlap among the three types of tasks.

Similarly, but focusing on left frontal regions, Lindenberg et al. (2007) conducted a cluster analysis of 311 activation peaks (coming from 119 reports), and whereas the peaks clustered into three anatomical regions, there was no systematic relationship between function (phonology, semantics, syntax, lip reading, finger movement, working memory) and these anatomical subregions.

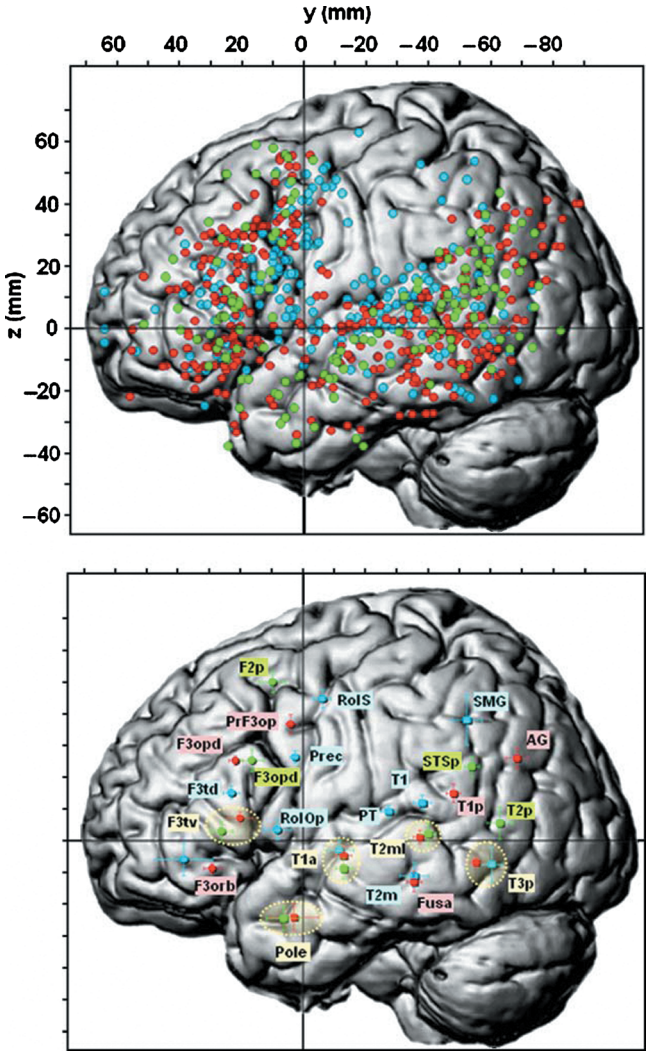

Fig. 1. Distribution of 730 activation peaks from 129 language studies: top panel – activation peaks for phonological (blue), semantic (red), and syntactic (green) tasks; bottom panel – results of a cluster analysis (from Vigneau et al. 2006) (reproduced with permission from *Neuroimage*).

These meta-analyses seem to indicate that language is supported by a widely distributed and only mildly (if at all) differentiated network of brain regions. In fact, Duncan and colleagues (Duncan and Owen 2000; Duncan 2001, 2004) have argued that little, if any, functional specialization exists with regard to the frontal lobes. Whereas the functional specialization view, whereby each brain region performs a very limited set of specific computations, is consistent with the cytoarchitectonic diversity of the frontal

lobes (Petrides and Pandya 1999, 2001; Nelissen et al. 2005), the alternative view, whereby brain regions have very broad functions and each region can perform multiple types of computations, is consistent with the connectivity patterns, which suggest extensive sharing and exchange of information (e.g., Duncan 2001). Based on the combination of human neuroimaging data and electrophysiology data from primates, Duncan and colleagues (Duncan and Owen 2000; Duncan 2001, 2004) have argued that neurons in the frontal lobes are highly adaptable, such that each neuron can be driven by many different kinds of input and thus perform a variety of functions.[3] However, before giving up the idea of functional specialization of the frontal and other brain regions involved in language processing, it is worth considering the possibility that at least some of the difficulty in mapping the relationship between brain regions and linguistic functions has been due to the fact that almost all neuroimaging research on language has so far relied on group analyses. We will now discuss the problems with this approach and argue for the use of an alternative approach in investigating the functional architecture of the language system in the brain.

Group Analyses and Brain Variability

The standard neuroimaging approach used to investigate the neural basis of language – as well as a number of other domains – involves aligning the data from each individual subject into a common space. In order to do so, brains are spatially normalized to a standard orientation, shape, and size into a stereotaxic coordinate system, such as the Talairach space (Talairach and Tournoux 1988). This process typically involves translating, rotating, scaling, and, sometimes, warping each individual brain to approximately match the template volume. This normalization procedure is problematic because of vast anatomical differences in cortical architecture (folding patterns) across individuals (e.g., Crum et al. 2003). To address this problem, Fischl and colleagues (e.g., Dale et al. 1999; Fischl et al. 1999a,b) have developed methods for co-registering individual brains that take into account the folding patterns. These methods involve 'unfolding' the cortex (turning it into a flat sheet or a sphere) and aligning each individual brain to an average cortical folding pattern created based on a large number of brains. While superior to the traditional normalization methods, these methods are still problematic, because of the variability in the locations of micro-anatomical regions (which presumably correspond to functional regions) with respect to gyri and sulci. This variability may cause activations to land in different locations across individual brains relative to gross cortical anatomy. As a result, even if two brains were very closely aligned in terms of their gyral/sulcal architecture, their functional activations may still not get aligned.

Group analyses extract only the collective effects of neural activations that are spatially overlapping across participants, potentially resulting in

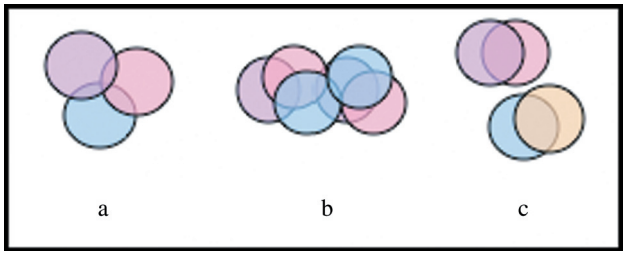

Fig. 2. Potential problems that may arise in group analyses. Different colors represent activations in different participants.

smearing activations across many millimeters, and even centimeters, of cortex, thereby obscuring the functional organization. The group analysis approach may lead to several types of errors (schematically illustrated in Figure (2a–c), where different colors represent activations in different participants): (i) some activations may not be detected due to no/little overlap across participants (Figure 2a); (ii) two adjacent but functionally distinct regions may appear to look like one region due to differences in absolute and relative locations of the two regions across participants (Figure 2b);[4] and (iii) one functional region may appear to look like two distinct regions due to a tendency of this region to land e.g., more anteriorly in some participants and more posteriorly in others (Figure 2c).

Of course, we are not the first to argue against the use of group analyses in investigating the neural basis of language. For example, Steinmetz and Seitz (1991) and Démonet et al. (1993) have argued against averaging data across participants in positron emission tomography (PET) studies of language. Furthermore, a similar debate took place in the aphasia community in the 1980s and 1990s. On the one hand, Caramazza and colleagues (e.g., Badecker and Caramazza 1985; Caramazza 1986; Caramazza and McCloskey 1988; Caramazza and Badecker 1989) were advocating the use of single-patient case studies in investigating the functional architecture of the language system. The main argument in favor of this approach concerns the variability present in the patient population and the resulting limitations in the conclusions one can draw from averaging the performance across multiple patients. On the other hand, a number of researchers (e.g., Zurif et al. 1989; Robertson et al. 1993; Grodzinsky 2000; Dronkers et al. 1994) have defended the group (syndrome-based) approach. The main arguments against the single-patient approach concerned the generalizability of the results. This debate never got resolved: no feasible solutions have been proposed that would satisfy both sides.[5] As discussed below, with regard to functional neuroimaging, the individual-subjects functional localization approach has the potential of both (i) circumventing the issues of variability, and (ii) avoiding the potential concerns with non-generalizability of the findings from single individuals.

Anatomical Variability

In discussing anatomical variability, it is useful to distinguish between variability at the macro level, which concerns differences in the gyral and sulcal anatomy, and variability at the micro level, which concerns differences in the mapping between gross cortical architecture and cytoarchitecture.

MACRO LEVEL

Variability at the macro level of brain anatomy concerns differences in the overall size and shape of the brain and in the characteristics of gyri and sulci. Differences among individual brains have been observed with regard to at least the following properties of gyri/sulci: (i) the size, shape and location of gyri and sulci; (ii) the depth of sulci; (iii) the presence/absence of sulci; (iv) the number of segments of a sulcus; (v) the number and position of side branches (e.g., Geschwind and Levitsky 1968; Ono et al. 1990; Duvernoy 1991; Zilles et al. 1997; Amunts et al. 1999; Tomaiuolo et al. 1999; Juch et al. 2005).

Tomaiuolo et al. (1999) examined 50 brains of right-handed individuals using magnetic resonance imaging (MRI), focusing on the properties of the pars opercularis of the inferior frontal gyrus, the part of the gyrus located between the inferior precentral sulcus and the vertical ramus of the Sylvian fissure and considered to be a part of the Broca's area. Considerable variability was observed in the shape of the structure, such that in some brains almost the entire structure was visible on the surface of the brain, appearing as a single convolution or two small convolutions, and in other brains, the pars opercularis was partially or completely hidden in the inferior precentral sulcus.

With regard to sulci, Juch et al. (2005) examined the extent of anatomical variability of the sulci located on the lateral frontal lobe surface. All the sulci examined were highly variable in length, orientation, and side branch patterns across individual brains (see Figure 3). Even the relatively stable landmarks (end points of sulci/connection points between pairs of sulci) exhibited variability of up to approximately 6 mm.

Furthermore, the vertical branch of the Sylvian fissure and the diagonal sulcus are variable in shape and may even be absent. The diagonal sulcus is reported to be present in only 12.5% of the right hemispheres (Geschwind and Levitsky 1968) and in 72% of the left hemispheres (Ono et al. 1990). More recent data from Amunts' lab suggests that the diagonal sulcus is present in only half (9 out of 20) of the hemispheres examined (Amunts et al. 1999).

MICRO LEVEL

Variability at the micro level of brain anatomy concerns differences in the location of cytoarchitectonic areas relative to the gyral/sulcal anatomy (e.g.,

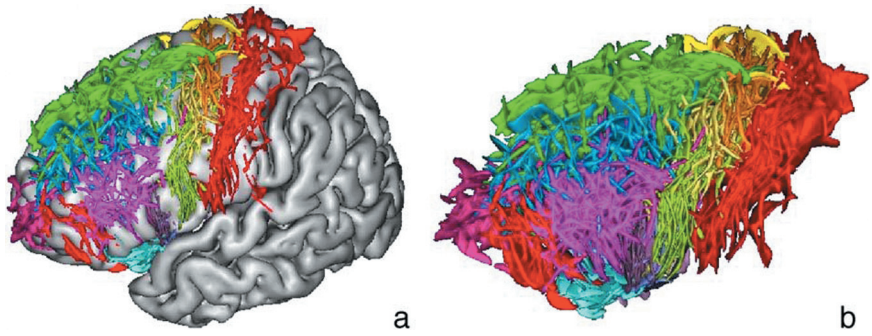

Fig. 3. The sulcal variability (a) superimposed onto a brain surface, and (b) without underlying grey matter (from Juch et al. 2005). Different colors represent different sulci in the frontal lobes. Individual lines represent the sulci in individual participants (reproduced with permission from *Neuroimage*).

Amunts and Willmes 2006). The cortical surface can be parcellated into a number of areas, based on cyto-, recepto-, and myelo-architecture, as well as connectivity patterns (e.g., Amunts and von Cramon 2006). These areas are plausible candidates for specific brain functions and therefore have always been of interest to cognitive neuroscientists. The early parcellation maps of the human cortex were created by staining histological sections of postmortem brains for cell bodies and examining changes in the size and distribution patterns of cell bodies, in cell densities, etc. (Brodmann 1909; Sarkisov et al. 1949). Recent advances in neurobiology have allowed for more objective, observer-independent methods involving quantitative evaluations of local changes in cytoarchitecture (Hudspeth et al. 1976; Haug 1979). However, while the cytoarchitectonic maps keep improving and getting more detailed and sophisticated, the usefulness of cytoarchitectonic areas in functional neuroimaging is limited because their locations with respect to gyral/sulcal architecture differ widely across individuals, and the current resolution of fMRI cannot get below the gross cortical architecture.

As early as in the beginning of the 20th century, Brodmann observed a high degree of inter-individual variability, particularly in regions dedicated to higher-order processes (i.e., the association cortices) (Brodmann 1909; see also Ono et al. 1990; Zilles et al. 1997). He reported that many cytoarchitectonic areas (that he assumed roughly corresponded to functional regions) bear no consistent relation to visible macroanatomic landmarks. Subsequent studies of human cytoarchitecture have continued to provide evidence along these lines (e.g., Clark 1993; Gebhard et al. 1993).

Amunts et al. (1999) reported, for example, that the border between BA44 and BA6 is highly variable: Its location varies between the rostral and the caudal walls of the precentral sulcus, which means that it differs with respect to the fundus of the sulcus by 1–2 cm. It was further reported that in some hemispheres the border between BA44 and BA45 is located

near the ascending branch of the lateral fissure, but in other hemispheres it is close to the diagonal sulcus, or interposed between the two sulci. The location of the cytoarchitectonic borders with respect to the sulci is also different between the two hemispheres within a single brain. Sherwood et al. (2003) reported similar variability in the location of BA 44 relative to anatomic landmarks in our closest living relatives, the great apes. In summary, there appears to be little, if any, consistent relationship between the borders of these cytoarchitectonic zones and gyral/sulcal anatomy. Similar results have been reported for other brain regions: for example, for inferior parietal sulcus (Caspers et al. 2006), BA 17 and BA 18 (striate and parts of extrastriate cortex) (Amunts et al., 2004), and amygdala, hippocampus, and entorhinal cortex (Amunts et al. 2005).

Fischl et al. (2008) recently directly compared several cytoarchitectonic areas with respect to how well their borders correspond to cortical folding patterns. It was observed – consistent with previous observations (e.g., Brodmann 1909; Rademacher et al. 1993) – that cortical folds are reasonably good predictors of the borders of the primary and secondary brain areas (e.g., the average error in boundary estimation for the primary visual cortex area V1 is approximately 3 mm). In contrast, predicting the borders of higher-order areas based on cortical folds is more difficult (e.g., the average error in estimating the boundaries of Brodmann area 44 is approximately 8 mm).

Functional Variability

Functional variability refers to differences in the location and size of language-sensitive regions across individuals. In evaluating issues of functional variability, it is a reasonable (though untested) working assumption that a stable correspondence exists between microarchitecture and function, such that if a particular cytoarchitectonic zone (characterized by particular cell types, density level of cells, myelination level of cells, etc.) performs some function *x* in one individual, then this cytoarchitectonic zone also performs the same function in another individual. Given this assumption, functional variability is a predicted consequence of macro- and microanatomical variability. In particular, as discussed above, because of the variability in the locations of microanatomical regions with respect to gyri and sulci, even if two brains were very closely aligned in terms of their gyral/sulcal architecture, the functional activations may still not get aligned.

Evidence of functional variability with regard to language comes primarily from clinical research. In neurological disorders, such as intractable epilepsy and brain tumors, treatment often requires removal of sections of cortex. When the necessary resection is located in proximity to potentially important cortical regions – like those responsible for language – it is essential to perform some form of functional-anatomic mapping in individual brains,

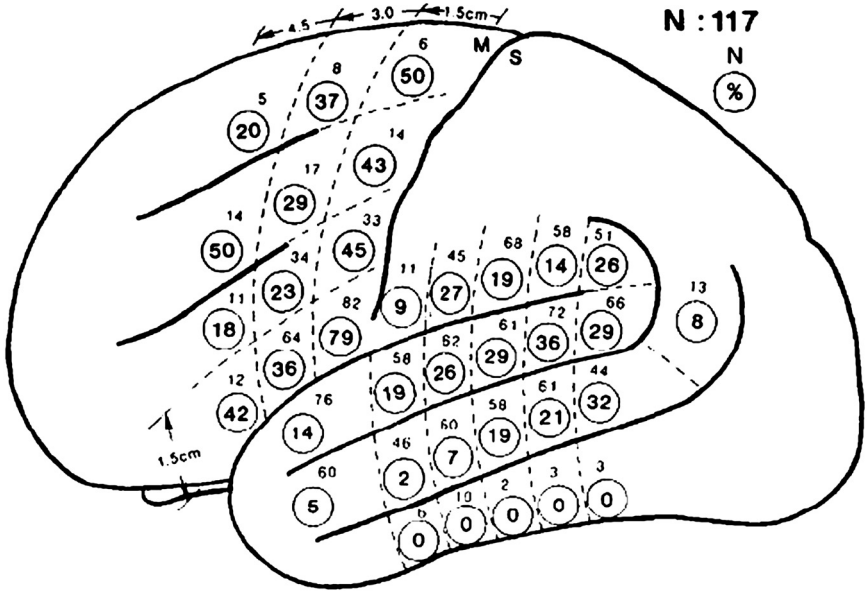

Fig. 4. Intraoperative stimulation data demonstrating individual variability of cortical sites essential for naming in the left, dominant hemisphere in 117 patients (from Steinmetz and Seitz 1991; data from Ojemann et al. 1989). Numbers in the circles are percentages of patients with an evoked naming error following stimulation of that area; numbers above the circles are numbers of patients stimulated in that area (reproduced with permission from *Neuropsychologia*).

in order to minimize postoperative deficits. The traditional tool for performing this mapping is electrocortical stimulation mapping (ESM), which involves applying electrical currents directly to the surface of the brain while the patient performs a cognitive task. Direct cortical stimulation induces a local temporary lesion that disrupts the normal functioning of that region of cortex. For example, if stimulation of a certain cortical region disrupts the patient's ability to perform a language task, it is considered 'essential' for language function. ESM has been used successfully for many years. This method provided some of the earliest evidence of inter-subject variability in the location and extent of language-sensitive regions (e.g., Penfield and Roberts 1959; Ojemann and Whitaker 1978; Ojemann 1979, 1983; Ojemann et al. 1989). For example, Figure 4 shows a summary analysis of ESM performed on 117 patients during a naming task[6] (Ojemann et al. 1989). Numbers in the circles indicate percentage of patients in whom stimulation to this site caused interruption (difficulty/errors) in performing the task.

As the figure demonstrates, stimulation at sites located across almost the entire temporal lobe and a large portion of the frontal lobe (in the dominant, left, hemisphere) can disrupt performance on the naming task. Some of this variability (for example, the fact that both the frontal and the temporal lobes are involved) plausibly has to do with the complexity of the task. In

particular, the naming task, as well as other tasks standardly used in ESM, potentially taps many different aspects of language (and non-language functions such as visual recognition)[7] and therefore plausibly engages multiple, possibly distinct, functional regions that may be located quite far from one another. However, any residual functional variability is an expected consequence of underlying anatomical variability.

With the development of PET and fMRI, clinical researchers began attempts at combining ESM with preoperative imaging, with the hope of the latter eventually replacing the former, which suffers from several serious limitations, including being highly invasive (see e.g., Bookheimer 1997, for a discussion of the limitations of ESM). Since the early 1990s, clinicians have been working on developing a standard brain imaging protocol for identifying key language regions in individual brains. Multiple studies have been conducted evaluating reliability of PET/fMRI in individual subjects (e.g., Herholz et al. 1996; Bookheimer et al. 1997; Xiong et al. 2000; Brannen et al. 2001; Ramsey et al. 2001; Rutten et al. 2002a,b; Fernandez et al. 2003; Stippich et al. 2003; Seghier et al. 2004; Harrington et al. 2006), or directly comparing the results of ESM and PET/fMRI (e.g., Fitzgerald et al. 1997; Rutten et al. 1999). The results of these studies have been informative in at least two ways. First, consistent with the earlier ESM data, they have revealed inter-subject variability in the location, extent, and intensity of functional activations. For example, Fitzgerald et al. (1997) compared ESM maps and activation data from five fMRI language tasks, and observed variability across subjects within each task, as well as across tasks within each subject. Similar to the ESM data, the reported functional variability is plausibly due to a combination of (i) anatomical variability, and (ii) complexity of the language tasks employed. But second, the results of these studies established that functional localization with fMRI is possible in individual subjects. For example, Stippich et al. (2003) demonstrated that with only 8 minutes of scanning it was possible to localize the traditionally implicated areas in left frontal and left temporal regions in individual brains.

In summary, on the one hand, the presence of functional variability – plausibly resulting from underlying differences in macro-anatomy and in the mapping between micro-anatomy and cortical folds – implies that aligning data across individuals may obscure the functional organization of language. But on the other hand, the robust activations for a variety of language tasks used by clinicians have established the feasibility of identifying language-sensitive regions in individual subjects, which is at the core of the approach proposed here.

An Alternative Approach: Functional Localization in Individual Subjects

The approach advocated here that circumvents the problems of inter-subject variability involves functional localization in individual subjects. As

discussed above, standard group analyses face at least two challenges. First, the inter-subject differences in gyral and sulcal architecture make transformation of individual brains into a stereotaxic coordinate system difficult. And second, the inter-subject differences in the mapping between cytoarchitectonic areas and gyral/sulcal landmarks further complicate the process of aligning individual brains in a common space, because even if it were possible to very closely align brains in terms of the macro-architecture, the underlying micro-architecture (and consequently functional activations) would still not line up. These problems undermine the idea of defining functional regions based on macroanatomy (even if done in individual subjects). It is possible that with the advances in magnetic resonance physics, it would one day be possible to identify and investigate distinct micro-anatomical regions. In the meantime, functional localization provides an alternative solution.

The functional localization approach entails three steps. The first step involves identifying a region/a set of regions of interest (ROIs) in each individual brain using a contrast aimed at isolating the cognitive process/type of representations of interest. For example, retinotopic visual areas V1, V2, and V3 are identified by comparing the fMRI response to visual checkerboard stimuli presented at different visual field locations to no-visual-stimulation conditions (Sereno et al. 1995); visual motion area MT is defined as the region that responds more to moving versus stationary dot arrays (Tootell et al. 1995); the fusiform face area (FFA) is defined as the region that responds more strongly to faces than objects (Kanwisher et al. 1997; see also McCarthy et al. 1997). The second step involves testing a specific hypothesis about the ROI(s) by examining its/their response to some set of relevant conditions. For example, one might want to investigate whether the region in question is sensitive to a particular distinction (e.g., whether the FFA's response is different for upright versus inverted faces (Kanwisher et al. 1998), or how selective the region's response is for particular types of stimuli (e.g., whether the FFA only responds to faces, or to other categories, as well (see Kanwisher and Yovel in press, for a review of the findings). The final third step involves averaging the responses of the ROIs to the target conditions across participants, to ensure that the results generalize. Occasional misunderstandings arise with regard to this last step, possibly because of the name of the approach (the individual-subjects functional localization approach). The 'individual-subjects' part of the name refers to the fact that ROIs are functionally identified in *individual* brains, without normalizing them and transforming them into a common space. However, group-level statistics are performed on the ROIs' responses to the conditions of interest. In this respect, the individual-subjects functional ROI approach is superior to single-patient case studies from neuropsychology, because a good localizer task will yield reliable activations in most participants, and the results will therefore be generalizable.

It is worth noting that a traditional group analysis can, and often should, be performed in addition to examining the responses of the ROIs

functionally defined in individual subjects. In fact, when a clear functionally specific region obtains in a group analysis, this constitutes a strong result. The problems of group analyses discussed in this paper are reasons why functional dissociations present in each subject might not be visible in a group analysis; they are not reasons to doubt a functional dissociation that does emerge in a group analysis. Furthermore, when interpretable results obtain in a group analysis, this provides a useful anatomical constraint on the interpretation of functional localizer data in individual brains. In particular, the group data can be used to decide which functional activations in different subjects should count as the 'same' ROI. Clearly, if the functional activations are in different lobes of the brain, that should not be considered the same ROI. But how close is close enough? An ideal solution would involve (i) identifying the regions of interest in individual participants, (ii) performing the standard group analysis finding spatial overlap across participants (perhaps at a rather permissive threshold), and (iii) using the intersection of the group ROI and the individual's ROI for each participant. Unfortunately, however, this solution will not always work. For example, the FFA might not be visible (or might be weak) in group analyses (unpublished data from the Kanwisher lab) despite the fact that it can be reliably localized in virtually all individual brains. As functional localizers become more commonly used in investigating higher-level cognitive processes, other quantitative anatomical constraints will have to be developed. For now, it seems reasonable to use gyral/sulcal architecture as guidelines for determining whether a particular functional region is plausibly in the same location across individuals.

The history of functional imaging of the ventral visual 'object vision' pathway over the last 15 years provides a striking illustration of the obscure picture that initially emerged from early group analyses (Figure 5) and the much clearer picture that emerged from later studies using the individual-subjects ROI approach (Figure 6). Aguirre and Farah (1998) reported a meta-analysis of 17 studies that all used group analyses and reported their activation peaks in the Talairach space. In particular, they examined studies that compared activations in response to three visual categories (objects, faces, and words) compared to low-level visual baseline conditions (e.g., fixation or scrambled images). The results of their meta-analysis are presented in Figure 5. These results look strikingly similar – in terms of the lack of clear clustering by function – to those reported in Vigneau et al.'s (2006) meta-analysis of language studies.[8]

Over the past decade, the use of the individual-subjects functional localization approach in investigating the neural basis of high-level vision has uncovered the fine-grained structure of the extrastriate visual cortex[9] (see Kanwisher 2003, for a review), revealing considerable specificity of different regions' responses to particular visual categories (e.g., FFA's selectivity for faces, visual word-form area's selectivity for written word forms, etc.). Figure 6 illustrates some of the functional regions that have been discovered and characterized using the individual-subjects analyses.

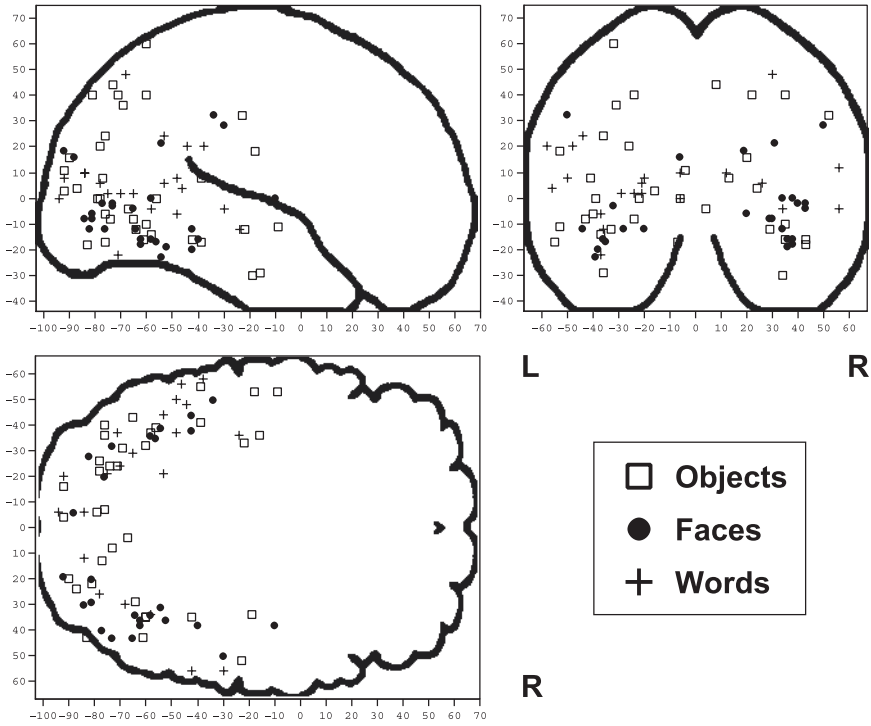

Fig. 5. Distribution of activation peaks, classified by stimulus type (from Aguirre and Farah 1998) (reproduced with permission from *Psychobiology*).

In addition to circumventing the problems of anatomical variability, functional localization offers several other advantages worth discussing briefly. First, using functional localization leads to an increase in statistical power. In particular, by predefining a set of voxels for which a particular hypothesis will be tested, the search space is substantially reduced, increasing the sensitivity of the statistical tests thereby allowing researchers to investigate potentially subtle aspects of the region's functional profile. And second, this approach increases the probability of discovering functional selectivity. In particular, in group analyses, the relevant region (the group ROI) will inevitably (i) miss some of the voxels sensitive to the relevant contrast in individual participants, and (ii) include some of the voxels not sensitive to the relevant contrast in individual participants. Both of these factors can misleadingly reduce selectivity (see Saxe et al. 2006, for a detailed discussion of these and other advantages of the individual-subjects functional localization approach; see figure 2d in that article, for a direct comparison of the response profiles of a group ROI and of the average response of the ROIs defined in individual participants).

Whereas the functional localization approach has been used for many years now by researchers investigating early sensory areas, such as V1, its

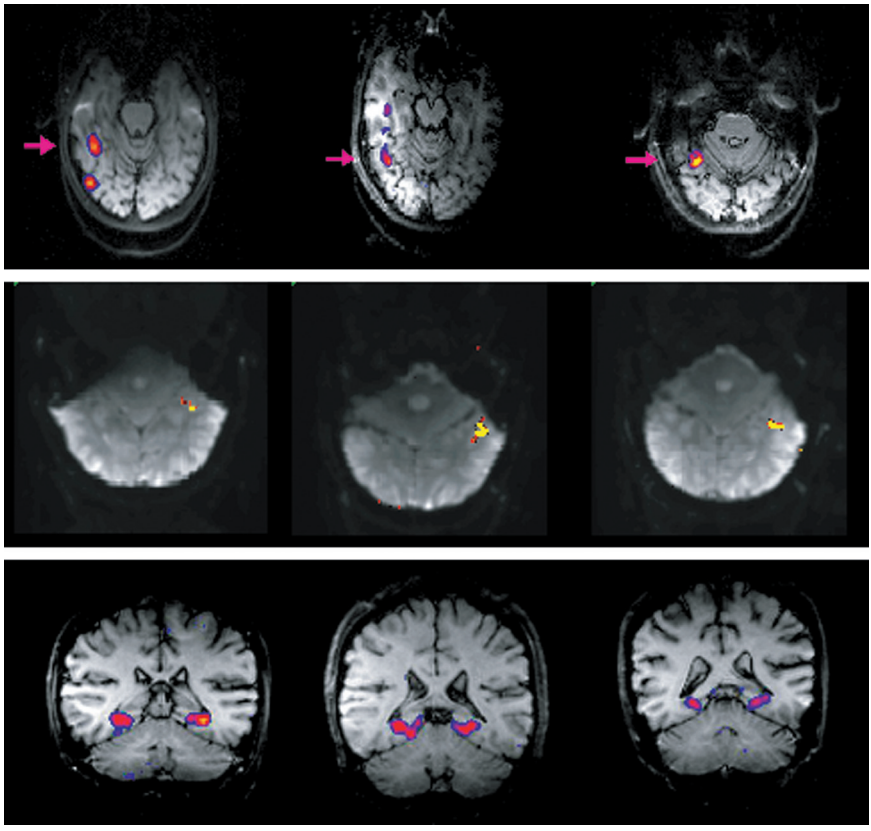

Fig. 6. Three of the functionally specific regions that have been discovered using the individual-subjects functional ROI approach. Top panel: the fusiform face area (FFA), which is defined by a higher response to faces than objects shown in three individual subjects (data from Kanwisher et al. 1997). Middle panel: a word and letter-string selective region, which is defined by its higher response to visually presented words than line drawings of objects shown in three individual subjects (data from Baker et al. 2007). Lower panel: the parahippocampal place area (PPA) which is defined by a higher response to scenes than objects shown in three individual subjects (data from Epstein et al. 1999).

use is still quite limited among researchers investigating high-level cognitive processes. One challenge for applying this approach to higher cognition concerns devising 'localizer' tasks that would selectively target the cognitive process/type of representations of interest and that can reliably identify the region(s) of interest in individual participants in a relatively short time. Whereas such tasks seem relatively straightforward for sensory processes, it gets increasingly difficult to decide on the relevant contrast, as cognitive processes get more complex. However, difficult does not mean impossible. As discussed above, functional localization has been highly successful in studies of higher-level visual processing (see Kanwisher 2003, for a review). And more recently, Saxe and Kanwisher (2003) applied functional localization

to the domain of social cognition by developing a localizer task that reliably identifies a set of regions that are involved in thinking about other people's minds. In the past several years, Saxe and colleagues have been investigating the functional profiles of these regions, focusing on the right temporo-parietal junction, which appears to be most selective for theory of mind. For example, some questions investigated so far include the functional specificity of these 'theory of mind' regions (Saxe and Wexler 2005), the involvement of these regions in moral judgments (Young et al. 2007; Young and Saxe 2008), and the similarity of these regions' responses in sighted versus blind individuals (Bedny et al. 2008).

The successful use of the functional localization approach in a higher cognitive domain (social cognition) is encouraging when evaluating the potential promise of this approach for language. Furthermore, as discussed above, the fact that some clinical studies have shown that language-sensitive regions can be localized in individual subjects with fMRI is also encouraging. However, the tasks typically used in clinical studies are not ideal as functional localizers for at least two reasons. First, because the goal of clinical studies is not to answer theoretical questions about the functional organization of the language system, but rather to localize all of language-sensitive cortex, the tasks typically used in clinical studies are not aimed at isolating particular aspects of language. And second, generalizability of the results beyond a single individual is not a concern in the clinical literature. For example, if a particular language task is highly susceptible to different strategies and activates different sets of regions across individuals, this is not a problem for clinical studies, as long as the regions critically involved in language are included in this set. As a result, cognitive neuroscientists will have to develop new localizers for language functions.

In devising functional localizer tasks for high-level cognitive domains, like language, there will always be a trade-off between selectively targeting a single aspect of the relevant domain on the one hand, and having sufficient power to detect reliable activations in individual participants in a short period of time, on the other hand. Because high-level cognitive processes involve many different components, no single localizer task will be well-suited for all purposes. Instead, it would probably have to be the case that multiple localizer tasks are used to ask questions about different aspects of linguistic processing.

In the past couple of years, we have made several attempts to develop functional localizer tasks for language, targeting the lexical/syntactic-level processing. We initially tried to develop several localizer tasks, each aimed at a particular aspect of language. For example, we tried using a standard syntactic complexity manipulation that has been successful in eliciting activations in group analyses (e.g., Stromswold et al. 1996; Caplan et al. 2006): the contrast between subject- and object-extracted relative clauses. Sentences containing object-extracted relative clauses (1b) involve a non-local structural dependency between the embedded verb ('attacked' in (1b)) and

its object ('the senator' in (1b)) and have been argued to require more working memory resources than their subject-extracted counterparts (1a) (e.g., King and Just 1991; Gibson 1998).

(1a) The senator that attacked the reporter was tall.
(1b) The senator that the reporter attacked was tall.

This contrast, while a nice minimal comparison and potentially useful at isolating a specific aspect of language (syntactic processing/syntactic working memory), unfortunately turned out to be not powerful enough to produce reliable activations in individual participants. We also tried using manipulations from Dapretto and Bookheimer (2002), who reported a dissociation between syntactic and semantic processing. We discovered that these contrasts are also not powerful enough to work in individual participants. As a result, we shifted to the use of larger contrasts.

As discussed above, some studies in the clinical literature have reported being able to localize language-sensitive regions (in the left frontal and temporal lobe) in individual subjects in a short period of scanning. We therefore attempted to find a compromise between manipulations targeted at very narrow aspects of language and the tasks used in the clinical literature. In other words, we tried to find contrasts that do not conflate too many linguistic/other processes, and yet are powerful enough for localizing language-sensitive cortex in individual brains. The localizer we developed (Fedorenko et al. in preparation) involves two contrasts that have been used in previous studies (e.g., Friederici et al. 2000): (i) the contrast between word lists and pronounceable non-word lists (targeting regions involved in processing word-level meanings), and (ii) the contrast between sentences and word lists (targeting regions involved in processing sentence-level meanings). This localizer reliably activates a set of regions[10] in individual participants in 10–20 minutes of scanning. Moreover, these regions appear in anatomically similar locations across participants, suggesting that we are looking at the 'same' regions in different brains. This localizer now allows us to ask questions about the functional profiles of these language-sensitive regions. In particular, we can investigate the functional specificity of these regions within the language system, as well as the extent to which these regions are specific to the domain of language.

In summary, the general robustness of activations for language tasks and the fact that the functional localization approach has recently been successfully applied in a very high-level cognitive domain (social cognition) suggest that the individual-subjects functional ROI approach holds considerable promise for investigating the functional architecture of the language system. We here mentioned one set of contrasts that appear to successfully target language-sensitive regions (for word and sentence-level processing) in individual participants. This is, of course, only a first attempt at applying the functional localization approach to the domain of language. Other localizers may later be developed for investigating these and other aspects of language.[11] One

challenge for the field will now be to carefully and systematically explore the functional profiles of various language-sensitive regions in order to develop a complete understanding of how language is implemented in the brain.

Summary and Conclusions

In this paper, we first summarized evidence for anatomical variability across individuals, in particular in the higher-level association cortices, which are critical for cognitive domains like language. We also reviewed some evidence of functional variability, which we argue results from a combination of (i) anatomical variability, and (ii) complexity of the language tasks employed in clinical studies, which is the primary source of data on inter-subject differences in the location of language-sensitive regions. On the basis of this review, and the fact that previous PET/fMRI studies have almost exclusively relied on group analyses, we argue that anatomical variability may be impeding progress in uncovering the neural basis of language using the neuroimaging methods. We propose applying the individual-subjects functional localization approach to the domain of language. This approach circumvents the problems of anatomical variability and has proven successful in uncovering the fine-grained structure of the extra-striate visual cortex (Kanwisher 2003) and, more recently, cortical regions engaged in social cognition (Saxe and Kanwisher 2003; Saxe 2006).

The use of group analyses for investigating language functions in the brain is certainly not the only problem that has impeded progress in our understanding of the neural basis of language; many factors are at play here. Some of these are outside of the investigators' control. For example, the existence of animal models in fields like vision, motor control, and memory has provided valuable insights into the functional organization of these domains and has helped guide neuroimaging research in humans. The lack of animal models for domains like language increases the difficulty of uncovering their neural basis. Other factors are fully under the investigators' control. For example, neuroimaging studies of language have been criticized on a number of dimensions, including both the theoretical aspects of the studies, as well as the methodological choices at the level of design, procedure and analysis (e.g., Kent 1998; Poeppel and Hickok 2004; Van Lancker Sidtis 2006; Caplan 2007; Geurts, unpublished manuscript). Nevertheless, there are three reasons why we wanted to draw attention to the possibility of using the functional localization approach in studying language. First, whereas methodological problems are common for neuroimaging studies across a wide range of cognitive domains, our understanding of the language system appears to lag behind many of these domains. Second, the use of the functional localization approach has been highly successful in uncovering the functional organization of a number of domains, including high-level visual processing and social cognition. And finally, the recent use of innovative methods in studying the relationship between macro- and micro-architecture

(e.g., by Amunts and colleagues) has highlighted the problem of anatomical variability and the need to move away from the traditional group analyses in studying the functional architecture of language and other high-level cognitive domains. All these reasons suggest that a new approach is needed in order to make progress in investigating the neural basis of language.

Developing functional localizers for different aspects of language should benefit both basic and clinical research. First, this approach has the potential to provide a roadmap of the functional organization of the language system, including a characterization of the functional properties and domain-specificity of each of the regions involved. And second, it could have important clinical implications. In particular, because of mixed results regarding the reliability of localizing language-sensitive cortex in individual subjects, clinical researchers agree that while fMRI can be used to determine hemispheric dominance, it cannot yet replace electrocortical stimulation mapping (e.g., Rutten et al. 2002b). Therefore, developing robust functional localizers should help identify components of the language system in individual brains as needed for preoperative localization of critical language regions.

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Short Biographies

Ev Fedorenko is a postdoctoral associate in the Kanwisher Lab at the McGovern Institute for Brain Research at MIT. She received her graduate training at MIT with Ted Gibson and Nancy Kanwisher. Her current work is aimed at investigating the neural basis of language using fMRI and other techniques. In particular, she is applying the functional localization approach, which has been successful in other domains, to language. This approach involves (a) functionally defining a set of regions involved in the domain of interest in individual brains, and subsequently (b) investigating the functional profiles of these regions. This approach circumvents problems of inter-subject anatomical variability, and may allow us to tackle important questions that have not yet been answered. She is also interested in the functional architecture of the language system more generally, working on a variety of questions related to the nature of language comprehension and production mechanisms.

Nancy Kanwisher is the Ellen Swallow Richard Professor in the Department of Brain & Cognitive Sciences at MIT, and Investigator at MIT's McGovern Institute for Brain Research. She received her B.S. in

1980 and her PhD in 1986, both from MIT. Kanwisher taught at UCLA and Harvard before returning to MIT in 1997. Kanwisher's lab has contributed to the identification and characterization of a number of regions in the human brain that conduct very specific cognitive functions: four are involved in the visual perception of specific kinds of stimuli (faces, places, bodies, and words), and another is selectively engaged in inferring the contents of another person's thoughts. Kanwisher received a Troland Research Award from the National Academy of Sciences in 1999, a MacVicar Faculty Fellow teaching Award from MIT in 2002, and the Golden Brain Award from the Minerva Foundation in 2007. She was elected as a member of the National Academy of Sciences in 2005 and the American Academy of Arts and Sciences in 2009.

Notes

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[1] It is not a goal of this paper to provide a comprehensive review of the findings from neuroimaging and other methods (e.g., aphasia or electrocortical stimulation mapping) potentially relevant to understanding the functional architecture of the language system. A number of such reviews – some focusing on particular aspects of language, others covering language more broadly – including meta-analyses of dozens of studies, already exist in the literature (e.g., Ojemann 1983; Petersen et al. 1988; Ojemann 1991, 1992; Démonet et al. 1993; Petersen and Fiez 1993; Kent 1998; Price 1998, 2000; Caplan 2001; Bookheimer 2002; Friederici 2002; Kaan and Swaab 2002; Friederici and Kotz 2003; Gernsbacher and Kaschak 2003; Martin 2003; Thompson-Schill 2003; Indefrey and Levelt 2004; Démonet et al. 2005; Stowe et al. 2005; Costafreda et al. 2006; Grodzinsky and Friederici 2006; Van Lancker Sidtis 2006; Vigneau et al. 2006; Caplan 2007; Caplan et al. 2007; Patterson et al. 2007; Lau et al. 2008).

[2] Just to mention a few regions for which some convergent evidence exists: (i) the left inferior frontal gyrus (LIFG) has been implicated in lexical retrieval (e.g., Thompson-Schill et al. 1997; Wagner et al. 2001), although recent evidence suggests that this region may not be specific to language and may rather be involved in general selection processes (e.g., Novick et al. 2005; January et al. in press); (ii) Brodmann areas 44 and 45 on the left inferior frontal gyrus have been consistently activated by syntactic complexity manipulations (e.g., Stromswold et al. 1996; Ben-Schahar et al. 2003; Caplan et al. 2006; Santi and Grodzinsky 2007; Caplan et al. 2008; Grodzinsky and Santi 2008); (iii) the anterior temporal lobe structures have been implicated in storing amodal conceptual representations (see Patterson et al. 2007, for a recent review; but see Lau et al. 2008, for concerns about this interpretation).

[3] Duncan et al. do not argue for the strongest version of this view (equipotentiality); rather, they propose a relative specialization view where any single cell can be more or less likely to represent different kinds of information or to perform different kinds of cognitive operations. As a result, different (but in many cases, overlapping) populations of neurons can be more or less likely to be engaged by different types of tasks, or by tasks in different domains.

[4] We are grateful to Jody Culham for pointing out that this issue is likely to get even worse for group studies, as the standards in the field are changing. In particular, it is now almost impossible to publish a group result without a random effects analysis. These analyses, while making the result generalizable to the population, have lower statistical power, which means that – in order to see significant effects – one either needs to get a large number of participants (which is often not possible because of the costs of fMRI) or smooth the data with a relatively large kernel (unpublished data from the Culham lab). Smoothing is problematic for investigating questions of functional specificity, as averaging across adjacent but functionally distinct regions can potentially result in an underestimate of selectivity.

[5] One non-feasible solution would involve averaging data across multiple patients with similar behavioral profiles, as determined by detailed investigations of each patient. This solution is not feasible because of the variability in the patient population resulting from differences in the location and extent of brain lesions.

[6] The task typically involves presenting the patient with a card which has 'This is a' written on it and a picture of a common object underneath. The patient is instructed to read the words aloud followed by naming the depicted object.

[7] For example, the naming task involves understanding the task demands, reading the sentence fragment, understanding the sentence fragment, preparing a set of motor commands to read the sentence fragment aloud, visual recognition of the depicted object, retrieving the relevant lexical item from long-term memory, inserting this lexical item into the syntactic frame, and finally, producing the complete sentence.

[8] It is worth noting that the two meta-analyses discussed here (Aguirre and Farah 1998; and Vigneau et al. 2006) do not take type of task into consideration, which likely exaggerates the across-studies variability. Meta-analyses, including some in the domain of language (e.g., Indefrey and Levelt 2004), that do take type of task into account tend to provide somewhat clearer pictures.

[9] Of course, improvements in the design of the studies (i.e. using more tightly controlled comparisons) are also a likely contributor to our increased understanding of the neural basis of high-level visual processing.

[10] Note that it is not a problem that *multiple* regions get activated by a functional localizer. In fact, this is likely to be true for most high-level cognitive processes; for example, Saxe's theory-of-mind localizer activates a set of five or six regions in most participants (e.g., Saxe and Kanwisher 2003). In studies combined with the localizer task, aimed at evaluating specific hypotheses about the functions of these regions, responses from each of the ROIs can be extracted and analyzed. In some ways, having a localizer that identifies multiple ROIs is even advantageous, as it allows investigating multiple functional regions simultaneously.

[11] For example, one recent study (Bedny et al. 2008) reported a set of regions that appear more highly active in response to verbs than nouns. The task is robust enough for individual-subjects localization (Bedny, personal communication) and is perfectly suited for investigating the neural basis of verb/event representations.

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