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# Modeling the Mind: High-Field fMRI-Activation During Cognition

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There are three signal events in the conceptual history of radiology. The first was obviously Roentgen's discovery of the use of x-rays to image tissue inside of the human body in 1895. The second conceptual event, which followed a short time later, was the realization that x-rays could be used to image not only anatomy, but also dynamic physiological function inside the human body. The significance of the latter event, by now incorporated in the knowledge of every educated person, is that the human life is supported by a vast network of interlocking physiological systems, such as the vascular and gastrointestinal systems. But in this article we will argue that a third conceptual development in radiology will ultimately provide the deepest insights into the nature of human life. This third event is the development of functional neuroimaging in the 1980's and 1990's, initially PET-based and now involving fMRI, which enables the imaging of the cortical functions subserving cognitive processing. Functional neuroimaging is capable of depicting not only physiological function in the brain, but also cognitive function. This latter meaning of "function" is the first medical and scientific opportunity to perform radiology not only on the brain, but also of the mind. In this article, we describe some of the properties of the cognitive systems that are beginning to be revealed with the use of high-field fMRI and consider some of the implications of these insights for scientific research and medical practice.

Because the central nervous system itself is dynamic, the emerging view from fMRI is beginning to accommodate these dynamics. "Dynamic" refers to two interrelated attributes: first, that the system changes over time and second, that energy transfer is a key principle underlying the observed patterns of change. For example, in sentence comprehension, dynamic cognition consists of information flow and computation at the level of the symbols that compose mental representations of words, phrases and meanings. In this paper, we will focus on the dynamics of high-level cognition and its cortical implementation as revealed by fMRI with paradigms that test high-level cognitive processes. Second, we will describe some simulation models that constitute theoretical descriptions of the dynamic properties of these systems. We begin by focusing on the language and spatial processing systems as model systems, but we propose that the principles are general, as we indicate below.

## The Cortical System Underlying Language Processing

### Cognitive function is subserved by large-scale networks.

Language function emerges not from the activation of a single brain area, but from large scale, information processing networks in the brain. Thus, a major research challenge in the functional neuroimaging of cognition is not just to identify which cortical areas are involved (although that is a necessary ingredient), but rather to determine how the multiple areas work together to achieve comprehension. The theory motivating the proposed experiments is that there is not a one-to-one mapping between cortical sites and comprehension functions. Rather, the system consists of interacting and hierarchically arranged subsystems that vary in the relative contributions that they make to particular computations and that map onto multiple cortical locations. The diagram in Figure 1 suggests that the mapping from brain site to behavior is not direct, but is mediated by an intermediate plane of computations that constitute the functional network (see Mesulam, 1990). Various computations are distributed across multiple cortical and subcortical sites. The distribution can be viewed as weighted (reflected in the varying thickness of the lines); one site may be a primary site for a particular computation, but other sites may also participate to lesser extents.

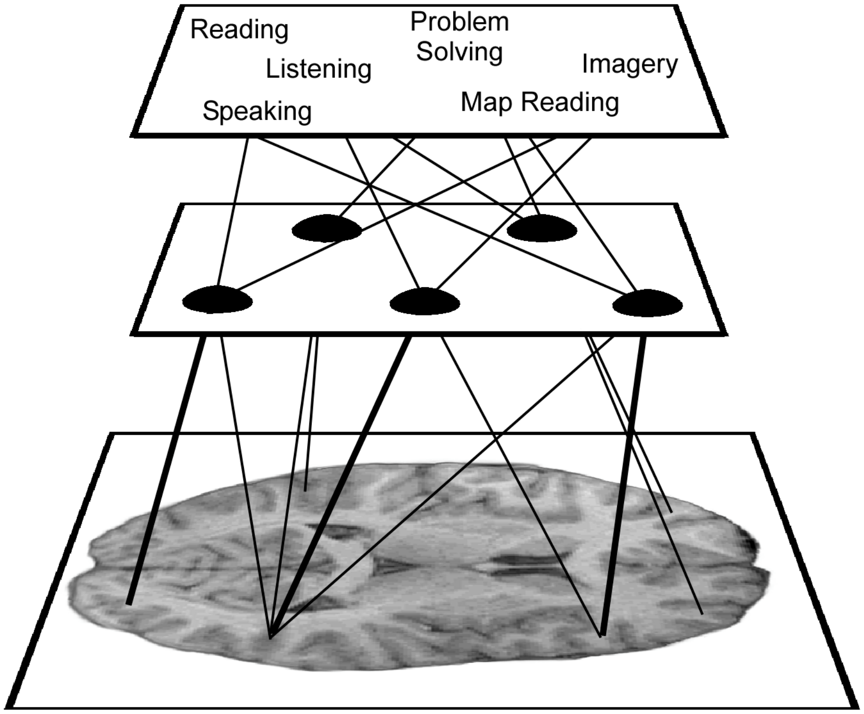


Figure 1. A figure schematically depicting the emerging conception of how cognitive performance, such as reading or problem solving, relate to cortical activity. Cognitive performance emerges from multiple levels of intermediate computations, for example, letter and word encoding, interpreting words and phrases, relating them to previous knowledge, and so forth. Each computation may map onto multiple cortical areas, although there may be a primary area that supports it, indicated by the thick lines. In addition, each cortical area may support multiple computations.

As a sentence like this one is being read, the activated networks includes the cortical systems supporting fundamental language comprehension processes, systems supporting the visual processing of the written words, and systems related to attention and the motor actions that guide visual attention and the concomitant shift of eye fixations. The distribution of activation in networks of cortical areas is graphically shown in the fourteen axial oblique slices in Figure 2, going from the top of the parietal cortex (the first, leftmost slice) down through the cerebellum. The figure shows the thresholded activation maps superimposed on structural images for a gradient echo, resonant echo planar MRI with BOLD contrast at 3.0T. It shows in white the voxels that are activated significantly higher when the participant read a sequence of sentences (typically, taking approximately 60 s overall) compared to a baseline condition in which the participant was simply fixating a point.

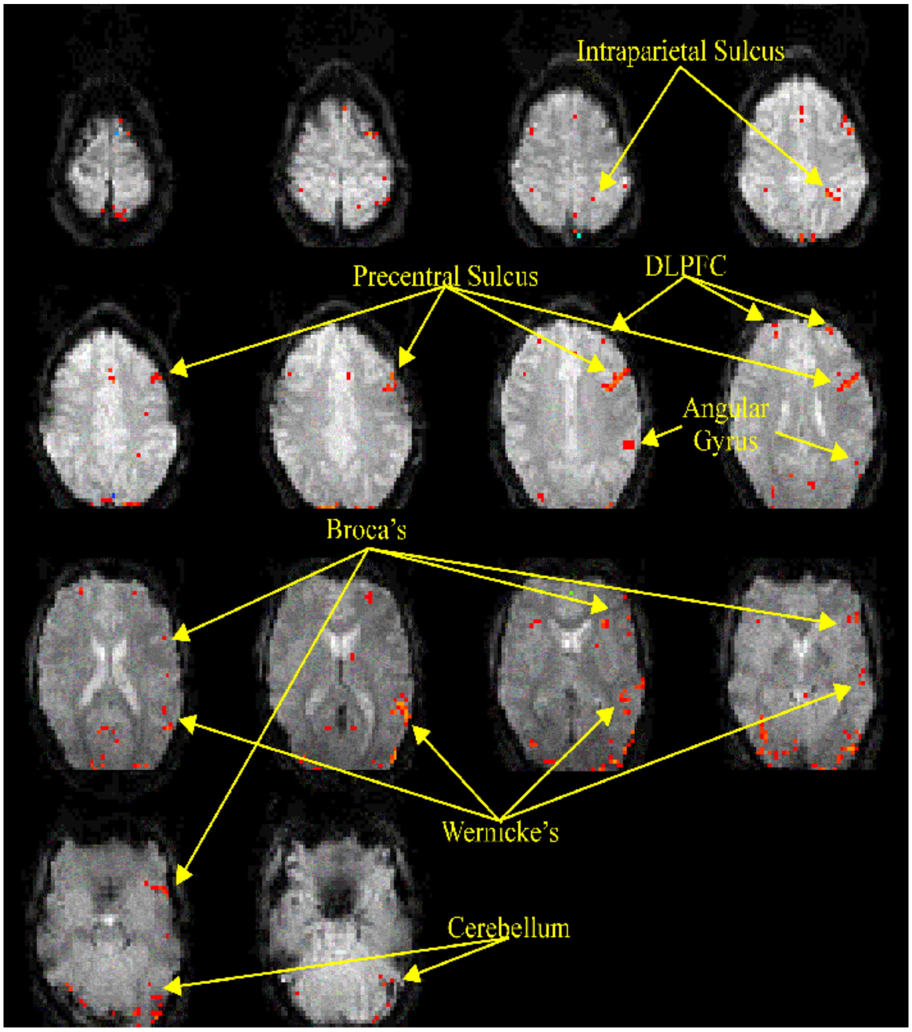


Figure 2. Statistical probability maps superimposed on structural images for a single individual to illustrate how a cognitive task (like sentence comprehension) elicits activation in multiple cortical loci. The voxels in white are those that are significantly activated above a baseline fixation condition when a normal college student reads a series of sentences. The 14 axial oblique slices were acquired with gradient echo, resonant echo planar MRI at 3.0T.

Two key cortical regions that are important for language comprehension are the left posterior superior and middle temporal gyri (roughly, Wernicke's area) and the left inferior frontal gyrus (Broca's area). Note that the activation in Broca's area and in Wernicke's area actually consists of several subregions across several slices, and for this particular task and individual, the activation is very left lateralized. The figure also shows activation in several areas related to visual processing, including activation in the primary visual areas and extrastriate cortex, in the posterior part of the slices in third row. Activation is also found in the angular gyrus, presumably also partially related to the visual processing of the text. The activation that is partially related to the shifting of visual attention and the concomitant execution of eye fixations during reading is in the parietal regions, particularly the intraparietal sulcus, and the supplementary motor region. The activation in the precentral sulcus may be partially related to motor aspects of reading because activation in these regions is often found in more purely motor tasks. However, its function may also include more cognitive functions, perhaps related to cognitive attention. Specifically activation in this region correlates with successful memory recognition for individual words (Buckner et al, 1998). Because the sentences (or the task) were conceptually demanding for this participant, activation is also found in the left middle frontal gyrus, labeled here as DLPFC (dorsolateral prefrontal cortex) on the slices in the second row. While we have described at least one major function associated with many of these regions, the specialization may only be relative and computations are probably distributed across multiple regions. The task is to understand how these multiple cortical regions work together in reading the printed letters and recognizing the words, constructing the syntactic and semantic interpretation of the phrases and clauses, and organizing a coherent representation of the sentence's meaning. This finding of a co-activation of a network of regions during a thinking task is evident in every fMRI study of language or of any other higher level cognitive function. It is a fundamental fact of brain function, which underlies all complex thinking. Although the empirical finding is not controversial, its interpretation raises a fundamental issue in functional neuroimaging, namely, the localization of cognitive functions.

**Cognitive function entails physiological work**.

A cognitive system that is challenged by a harder task compared to an easier version of the same task responds over the short term by recruiting more neural elements within the system and sometimes by recruiting other, related systems. One implication of this claim is that the localization of a function depends not just on what the cognitive system is doing, but also on how hard it has to work to do it. This conclusion and its implication contrast with an earlier assumption that the neural "hardware" is fixed. Instead, it suggests that within some bounds, the allocation is more dynamic and in part, it is a function of the task's demand

**Early functional imaging of the language system.**

Some of the early resting-state studies of aphasic patients provided some indications of both the network properties of the language system and its workload sensitivity. The network-related result, from several FDG-based PET studies, was that over 96% of the many tens of aphasic patients who were tested had a common site of metabolic impairment, a hypometabolism, in the left temporal and temporoparietal regions, measured when the patient was at rest and not performing any task (Karbe et al 1989; Kempler et al 1991; Metter et al.1990). It is remarkable that this generalization held regardless of the site of the structural lesion, including subcortical sites, and regardless of clinical categories of aphasia. The result that any aphasia-inducing damage ultimately changes the function of a common site indicates that a variety of regions participate in a network function that includes this common site.

Another fascinating aspect of these early PET results was that the degree of an aphasic patient's metabolic impairment (defined as the degree of hypometabolism) substantially correlated with the degree of impairment in sentence comprehension (measured off-line by standardized tests). For example, in one of these studies (Kempler et al 1991), the resting state cerebral glucose metabolic rate (which was hypometabolic) in the left temporoparietal regions (but not others) correlated with comprehension performance in a common test of aphasic language skill, the Western Aphasia Battery (WAB) ($r = .44$ for the laterosuperior temporal gyrus and $r = .60$ for the middle temporal gyrus, areas that include Wernicke's area.). This result speaks not only to the network properties of the language system, but also to the resource properties of the network. Specifically, the measure of resting PET activity may provide an index of the size of the patients' potential resource supply, which could place an upper limit on sentence comprehension. This interpretation is the basis of a computational model of aphasic sentence comprehension that we have developed with Henk Haarmann (Haarmann et al, 1997). The model can produce a semantic interpretation of a sentence and answer questions about the content of the sentence. The model's information processing functions consume resources, and the model's performance degrades as its resource pool is decreased. With inadequate resources, the model produces a partial representation of a sentence, the more so if the sentence is demanding. The model's degradation in comprehension performance with decreasing resources and with increasing sentence complexity provides a good match to the comprehension performance of aphasic patients who vary in the severity of their impairment. This earlier model was not a model of cortical function, because it treated the entire language system as a single entity rather than a network of collaborating areas. Nevertheless, the model captured the resource-sensitive nature of language processing, and it appropriately characterized the impact of differential severity of brain damage as differential resource depletion.

### An fMRI study of task demand in language system.

In an initial demonstration of the cognitive workload effect in the domain of language comprehension, we found that as sentence comprehension becomes more difficult because of syntactic and semantic features, there is an increase in the fMRI-measured activation in a network of cortical regions. These regions include the left perisylvian cortical regions that are classically associated with language processing and regions in the right homologue (Just, Carpenter, Keller, Eddy & Thulborn, 1996).

The amount of activation in four cortical areas (Wernicke's, Broca's, and their right hemisphere homologues) was examined in 15 normal right-handed young adults, as a function of the demand imposed by the comprehension of three sentence types. The sentences are superficially similar (each containing two clauses and the same number of content words) but they differ in structural complexity, and hence, in the demand they impose in the sense of how much processing is needed to figure out who is doing what to whom. To illustrate the surface structure similarities among the three sentence types, we've used the same words. However, in the study, each sentence had different words that had been randomly assigned to different sentence types.

1. **ACTIVE CONJOINED**
*The reporter attacked the senator and admitted the error.*

2. **SUBJECT RELATIVE CLAUSE**
*The reporter that attacked the senator admitted the error.*

3. **OBJECT RELATIVE CLAUSE**
*The reporter that the senator attacked admitted the error.*

Whereas type 1 sentences contain active clauses that are simply conjoined, the more complex type 2 sentences contain a relative clause that interrupts a main clause, causing additional maintenance. Finally, in type 3 sentences the main clause is interrupted, and the first noun plays different roles in the two clauses (as the subject of the main clause and the object of the relative clause). The most complex type (type 3, Object Relatives) produces longer processing times, higher error rates, and larger increases in pupil dilation (another measure of cognitive effort) than the less complex type (type 2, Subject Relatives) (Just & Carpenter, 1993; King & Just, 1991)

The experiment involved five different conditions. In conditions of type 1, 2, or 3, the participant read several different sentences of the appropriate type successively, and after each sentence, answered a visually presented question such as, "Who did the attacking?" In a fourth condition, intended to assess visual processing, the participant was shown a series of "nonsense" words made of consonant strings that they were to scan. In the fifth condition, the participant simply fixated an asterisk, and the activation during this condition provided a baseline against which all the other conditions were compared. On average, approximately 60 images were taken during each condition for each participant. In all of the analyses, the average activation level for each voxel in a region of interest (ROI) during the experimental conditions was statistically compared to the activation during the baseline conditions using a t-statistic to identify which voxels were significantly activated.

This earlier study of ours was done at 1.5 Tesla, using gradient echo, resonant echo planar MRI, with BOLD contrast. The acquisition parameters were TR = 1500 ms, TE = 50 ms, flip angle = 90°, voxel size = 3.125 x 3.125 x 5 mm, 7 axial slice planes, slice thickness = 5mm, 1mm gap, acquisition matrix =128 x 64, FOV = 400 x 200 mm. The images from more recent studies were obtained at 3.0T, changing the TR to 3000 ms and the TE to 25 ms. At both field strengths, TE was chosen to match $T_2^*$ to ensure maximum sensitivity of BOLD contrast. The larger TR at 3.0T allows more slices to be acquired to cover more of the brain.

Because our approach focuses on measuring the amount of activity in some area, it is important to have an a priori definition of a cortical area. That is, we ask the question “how is the activation modulated by task demand,” so we must know where to look for the activation. By contrast, other approaches that focus on the “where” question (what are the locations of the activation in such and such task) need only determine the centroids of activations, often done with respect to Talairach coordinates. Our approach makes use of anatomically defined regions of interest (ROI’s), which are drawn for each individual subject. It would be preferable to use a universal parcellation scheme that is based not only on structural properties of the brain but also on known functional (activation) properties as well, but unfortunately no such scheme yet exists. We use the anatomical parcellation scheme developed by Rademacher et al. (1992), one view of which is shown in Figure 3. This parcellation uses limiting sulci and anatomically landmarked coronal planes to segment cortical regions. To co-register the functional and structural images, a mean of the functional images is co-registered to a high-resolution structural volumetric scan (SPGR), and limiting sulci are identified by viewing the structural images simultaneously in the three orthogonal planes. The functional images are then segmented in the functional acquisition plane by manually tracing the regions of interest on each slice. To facilitate this tracing, we start with a template of the ROI that has been defined in a template brain, and then we transform those templates to fit each subject’s brain, adjusting them according to each subject’s structural landmarks. In the nomenclature of Rademacher et al. (1992), the area we refer to as **Wernicke’s area** includes areas T1p, T2p, TO2, PT and portions of areas SGp and AG (Brodmann’s areas 22, 37, 39, 40 and 42). (Area PT, planum temporale, is not visible in this figure). Figure 4 indicates a slice through part of this area in sagittal view for one participant. The area we refer to as **Broca’s area** corresponds to areas F3o, F3t, FOC and FO (Brodmann’s areas 4, 6, 44, 45, and 47). (Area FO is not visible in this figure). The **dorsolateral prefrontal** region corresponds to area F2 (Brodmann’s Areas 8, 9, and 46).

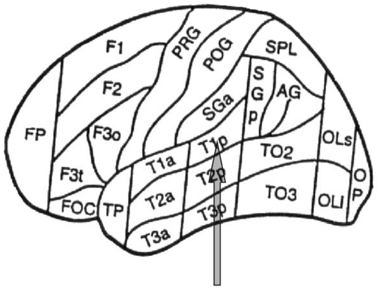


Figure 3. The anatomical parcellation scheme developed by Rademacher et al. (1992) provides a convenient way to refer to cortical regions when quantitatively assessing fMRI-measured activation. This view highlights an area of key interest in our studies of language comprehension. (Adapted from “Human cerebral cortex: Localization, parcellation, and morphometry with magnetic resonance imaging” by Rademacher, Galaburda, Kennedy, Filipek, & Caviness, 1992. *Journal of Cognitive Neuroscience, 4*, Figure 1, p. 354.)

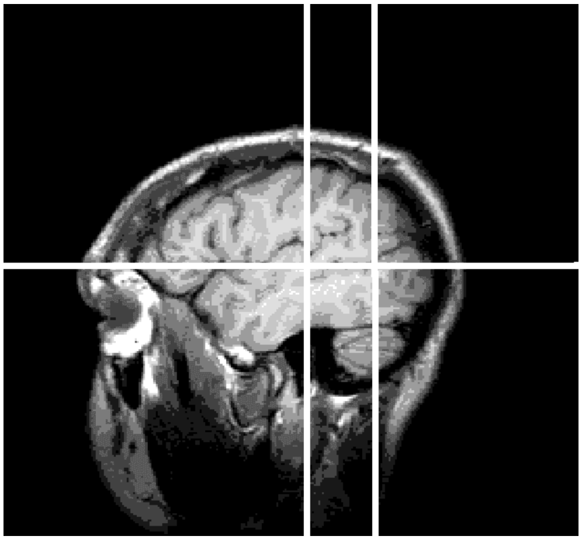


Figure 4. The sagittal scouts for a college student, indicating the axial slice that elicited the most activation in the posterior superior

temporal gyrus in a reading comprehension study.

Figure 5 shows the thresholded fMRI activation images (1.5T) superimposed on structural images for the most activated slice for one participant. Each image shows the results for one condition for this slice, showing in white the voxels that are significantly more activated than the resting baseline, using a *t*-test to compare the average activation level of each voxel in each sentence condition to its level during rest epochs. The structural image of the most active slice through Wernicke's area (indicated by the box). This particular slice shows little of the activation in the right homologue or in Broca's area or its right-hemisphere homologue. The increasing number of white voxels in the box illustrates how the number of significantly activated voxels increases as the complexity of the demand increases, that is, in going from consonant strings to simple conjoined active sentences, to sentences with embedded subject relative clauses and finally, to sentences with embedded object relative clauses. Because the activation in Broca's area was difficult to evaluate precisely given the location of the axial scans, the activation was assessed in five of the 15 participants (hence, the larger error bars) who were additionally scanned in an ancillary study using coronal slices and presenting comparable sentences. While this shows the effect for only one participant, the results were supported by the analysis of the volume of activation over the three most relevant slices across all of the participants.

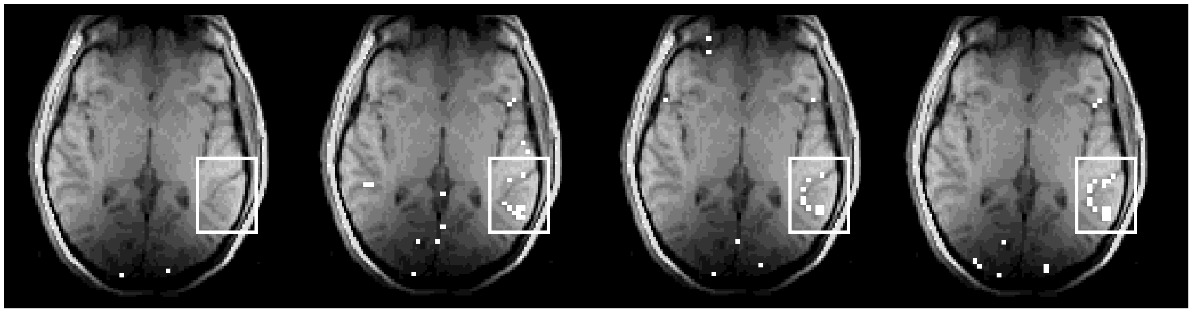

Consonant Strings Conjoined Actives Subject Relatives Object Relatives

Figure 5. Thresholded fMRI activation images (1.5T) (superimposed on structural images) for only the most activated slice through Wernicke's area (indicated by the arrow) from one participant. The number of activated voxels (shown in white) generally increases with sentence complexity. (From "Brain activation modulated by sentence comprehension" by Just, Carpenter, Keller, Eddy, & Thulborn, 1996, *Science, 274*, Figure 2, p. 115. Copyright 1996 by the American Association for the Advancement of Science. Reprinted with permission).

The results, after being aggregated over all the participants (as shown in Figure 6), indicate that the processing of more complex sentences leads to an increase in the volume of neural tissue that is highly activated in all four areas: Wernicke's area, Broca's area, and their right hemisphere homologues. We use the terms "Wernicke's area" and "Broca's area," but defined with respect to Rademacher's scheme, acknowledging that there are no clear cyto-architectonic boundaries. The increased activation also occurred in a second measure, the percentage of activation compared to the level in the fixation condition. The importance of the increase in activation is that it suggests that the language comprehension system responds to increased demand by increasing the areas that are involved (activation of the right hemisphere homologues) and increasing the contribution of activity within that region or adjacent regions.

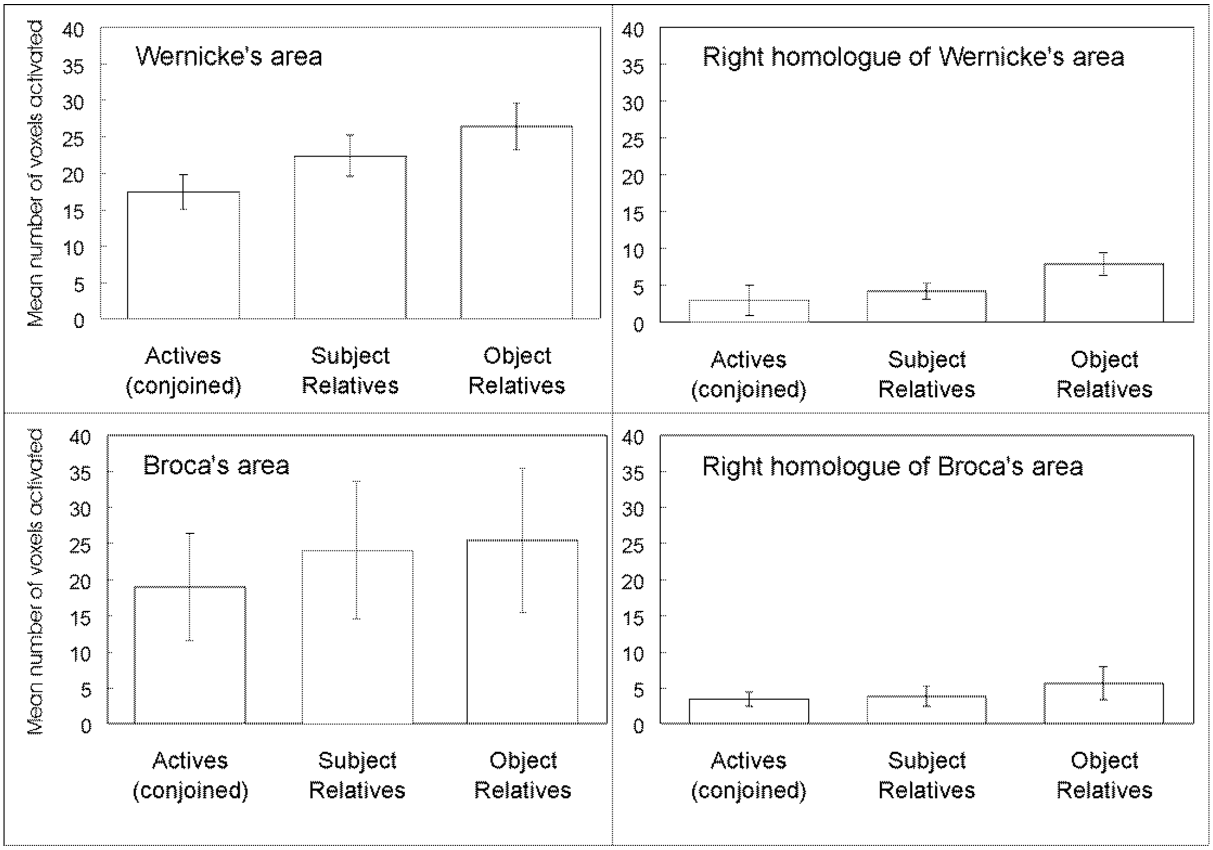


Figure 6. The average number of activated voxels across participants indicates that the processing of more complex sentences leads to an increase in the volume of neural tissue that is highly activated in all four areas. The top panels indicate the average number of activated voxels in the left (Wernicke's area) and right laterosuperior temporal cortex (and standard errors of the means over 15 participants). The bottom panels indicate the average number of activated voxels in the left (Broca's area) and right inferior frontal cortex (and standard errors of the means over only five participants). (From "Brain activation modulated by sentence comprehension" by Just, Carpenter, Keller, Eddy, & Thulborn, 1996, *Science, 274*, Figure 1, p. 115. Copyright 1996 by the American Association for the Advancement of Science. Reprinted with permission).

## A graphic display of the increase in activation with sentence demand.

The contour plots shown in Figure 7 simultaneously display topographic information and amplitude information. The plane corresponds to brain topography and the height of the points corresponds to the amplitude of the voxels' activation increases over baseline levels (actually, their *t* values, a proxy for their amplitude that controls for variance). The left-hand plots show the voxels' *t* values in the active (conjoined) condition, and the right hand plots show the most demanding object-relative condition, for the axial slice with the most activation. The three pairs of plots are data from three participants

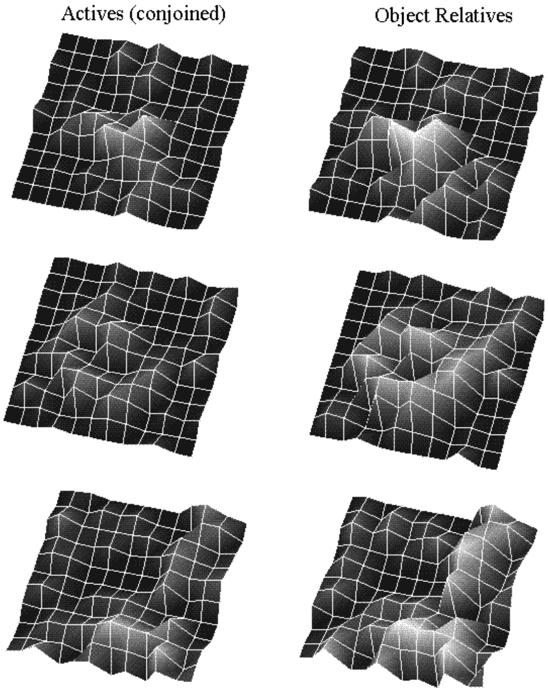


Figure 7. Contour plots that simultaneously display topographic information and amplitude information for the easier conjoined active sentences (left hand plots) and the harder object relative sentences (right hand plots). The plane corresponds to brain topography and the height of the points corresponds to the amplitude of the voxels' activation increases over baseline levels (actually, their *t* values, a proxy for their amplitude that controls for variance). The three pairs of plots are data from three participants. (From "Brain activation modulated by sentence comprehension" by Just, Carpenter, Keller, Eddy, & Thulborn, 1996, *Science, 274*, Figure 3, p. 115. Copyright 1996 by the American Association for the Advancement of Science. Reprinted with permission).

The mountain range of voxels that is activated in the active-conjoined condition appears to erupt further still in the object relative condition. The new voxels that become activated in the object relative condition tend to fill in and augment existing groups of activated voxels. The non-participating voxels are doing relatively little in both of these sentence conditions. So the effect of increasing the sentence demand is twofold. First, the increase in demand increases the number of activated voxels (by pushing to threshold voxels in the foothills and interstices of the mountain range that had been only partially activated in the less demanding condition). This effect occurs in a very large majority of the participants. Second, the increase in demand increases the activation level of some of the previously activated voxels. The latter effect occurs for a majority of the participants, but not a large majority. Thus, making the brain work harder on sentence comprehension increases the volume and the magnitude of its activation. Finally, these plots show that some of the activated voxels are spatially contiguous or nearby.

The contour plots suggest that as demand increases, adjacent and interstitial voxels that were near the threshold level now rise above the threshold level, and the already activated voxels increase their activation level. One interpretation of the increase in the volume of activation is simply that the increased demand causes a recruitment of additional neuronal tissue. Another interpretation is that some subvolume of the additionally recruited voxels had been activated even in the condition with the easiest sentences, but that the total activation in the entire voxel was not enough to bring it to the threshold level. Both interpretations entail that there is more brain activation for more difficult sentences.

The precise functions of the four regions are not delineated by this task, except to suggest that the additional processing is not lexical (given that lexical content was equivalent across conditions). The modulated activation of the right homologue of Wernicke's area is consistent with the proposal that it, too, is part of the language network, in addition to being evoked in the processing of figurative (non-literal) language (Bottini et al., 1994) and prosodic information (Tompkins & Mateer, 1985). Thus, language comprehension, like other cognitive attainments, is accomplished by a network that spans several cortical regions across both hemispheres, as well as subcortical regions that are not here the focus. More generally, this study demonstrates that the neural system activation does not reflect simply the qualitative nature of the demand, but also the amount of demand. To meet the increased demand as the difficulty of the task increases, the system recruits more regions.

### Reading compared to listening comprehension.

One reason to believe that the left posterior superior and middle temporal regions and the inferior frontal regions are involved in fundamental language comprehension processes is because these regions consistently show activation both in reading comprehension and in listening comprehension. To make this comparison, the task is kept the same as we described earlier, but instead of presenting the sentences in written form, they are presented auditorily, and the data for both conditions are acquired at 3.0T. Again, the activation in both the reading conditions and the listening conditions are compared to the activation of common baseline condition, in which the participant is simply fixating a point (Carpenter, Just & Keller, 1999). The patterns of activation in the two conditions show both commonalities and differences that can be illustrated with the data from one individual. Figure 8 shows two slices in an oblique axial orientation that include the middle and superior temporal regions for the reading condition (on the left) and the listening condition (on the right). The reading condition shows primarily left lateralized activation in the posterior superior and middle temporal regions, with only a little bilateral activation in the more superior slice, as well as activation in the more posterior visual regions. The listening condition shows no activation in the primary visual regions, but considerable bilateral activation, presumably partly associated with the early auditory processing. In addition, notice that there is considerable overlap in the patterns of activation, particularly in the left posterior middle temporal region, presumably due to the shared language interpretation processes supported by this neural region. The partial overlap suggests that computations subserved by this region are evoked in both comprehension tasks, irrespective of the modality.

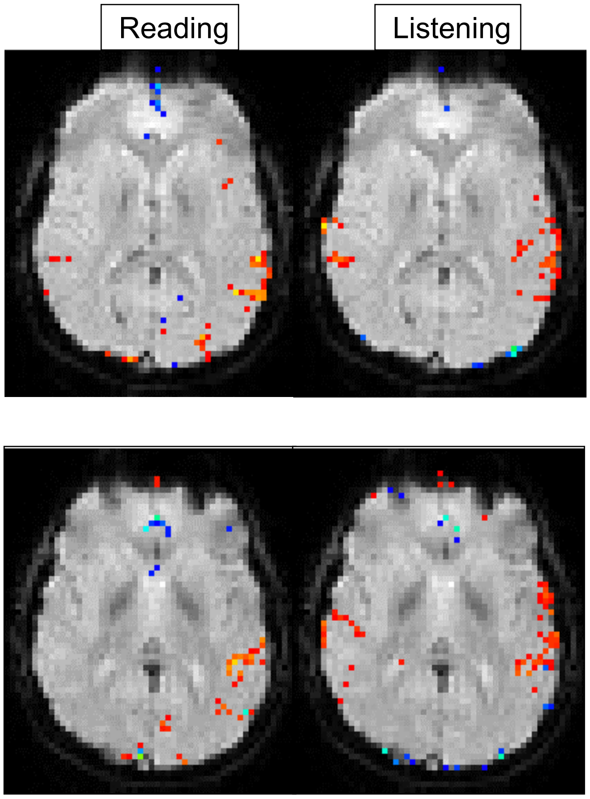


Figure 8. Two oblique axial slices (the more superior is the upper slice) that include part of the middle and superior temporal regions showing the activation in the reading (on the left) and the listening condition (on the right) for a single individual. The reading condition shows primarily left lateralized activation in the posterior superior and middle temporal regions, with a little bilateral activation in the more superior slice, as well as activation in the more posterior visual regions in both slices. The listening condition shows no activation in the visual regions, but considerable bilateral temporal activation, associated with the auditory processing. In addition, the overlap in the patterns of activation, particularly in the left posterior middle temporal region and to a lesser extent right temporal region, are presumably due to the language interpretation processes supported by these regions.

### Spatial resolution.

A fascinating aspect of high-field fMRI is that it reveals that cortical neural systems are organized at several different spatial grain sizes. While most of our studies have used a spatial resolution producing voxels that are approximately 48 $mm^3$ in volume (3.1 x 3.1 x 5 mm$^3$, this has become apparent in a few case studies done at a much higher spatial resolution, producing voxels that are approximately 0.8 x 1.6 x 3 mm$^3$ in volume (Thulborn, Chang, Shen & Voyvodic, 1997). These smaller voxels begin to approach the magnitude of a cortical column. The high-resolution studies are difficult to perform because they can tolerate less head motion than many participants can accommodate. Furthermore, the additional spatial resolution is bought at the expense of obtaining less coverage of the brain. However, at the high spatial resolution fMRI produces an additional brilliant level of detail, while retaining all the information produced by the lower resolution image. In collaboration with Tim Keller, we obtained a pair of images that contrasts higher and lower spatial resolution by studying the same person on the same sentence comprehension paradigm. Figure 9 shows that the high-resolution image of the activation in left superior temporal gyrus precisely follows the margin of the sulcus, whereas this level of detail is unavailable in the lower resolution image.

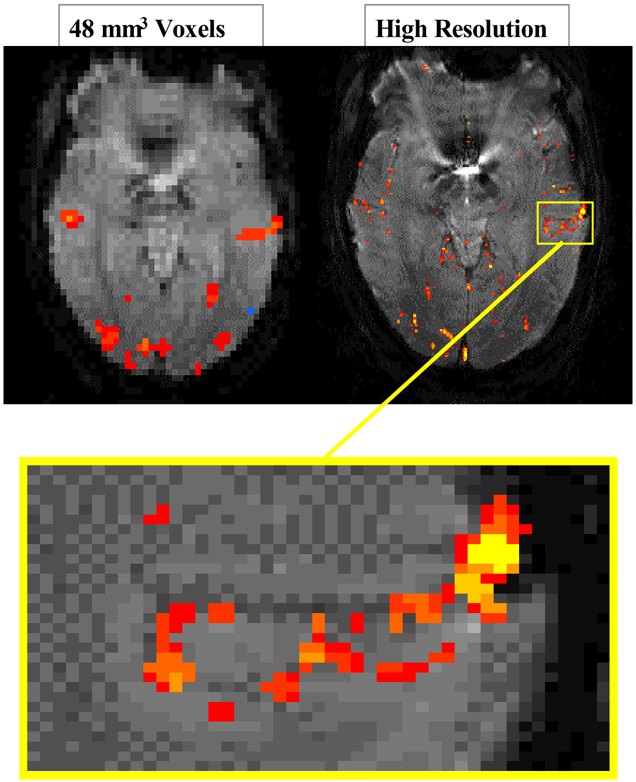


Figure 9. A comparison of the activation in the same slice obtained by studying the same person on the same sentence comprehension paradigm, but at different spatial resolutions. The cut-out from the high-resolution image (on the right) shows that the activation in left superior temporal gyrus precisely follows the margin of the sulcus, whereas this level of detail is unavailable in the lower resolution image.

One interpretation of the finer spatial resolution is that it is closer to the “truth” in the sense that the resolution may be closer to capturing the functional units of neural computation. However, an alternative view is that computation is occurring simultaneously at several levels, levels from small neural clusters within circumscribed regions of the cortex, on up to the large scale computations that emerge from the coordinated activities across multiple cortical regions. If this latter perspective is a more accurate one, then there is no ideal spatial resolution and ultimately, the theoretical account of cognition will need to span across multiple spatial as well as temporal grain sizes to account for how cognition unfolds in the brain.

### Clinical application.

We have had the opportunity to apply this fMRI paradigm to a surgical candidate, a patient with an arterio-venous malformation (AVM) in the left frontal cortex. The patient was a 38-year-old woman who presented with periods of word-finding difficulties and intense headaches. The patient’s comprehension accuracy was well in the normal range. Figure 10 depicts the activation results for the patient with the AVM from a study done in collaboration with Tim Keller and Keith Thulborn, along with the comparable data from a college student. For the college student, two of the main cortical areas are activated during sentence comprehension are in the left hemisphere (on the right of the image), reflecting the largely left-lateralization of language processing. The cluster at the top (anterior) is the left inferior frontal gyrus (Broca’s) and the cluster at the bottom is the posterior superior temporal gyrus (Wernicke’s area).

The image on the left from the patient demonstrates that this fMRI paradigm provides interpretable data concerning an abnormal language system. The AVM is visible as a large darkened region in the left frontal region. The images show normal activation in the left temporal region (Wernicke’s), but an abnormal lack of response in the left inferior frontal cortex

(Broca's area), presumably due to the AVM. Note that this image shows there is strong activation in the right inferior frontal cortex. While we have observed activation in the right homologue of Broca's area, such a strongly contralateral pattern of activation (right frontal and left temporal) is one that we have not observed in the testing of approximately 100 normal individuals, and it suggests that more of the language functions have been taken over by the right hemisphere than in the typical college student. Thus, the normal language network has been disrupted by the AVM, and the network function has been reconstituted with the right homologue of Broca's area playing a larger role in place of the damaged area. The more general conclusion is that the disruption of a network underlying cognition to which a patient adapts is produced by a network adaptation.

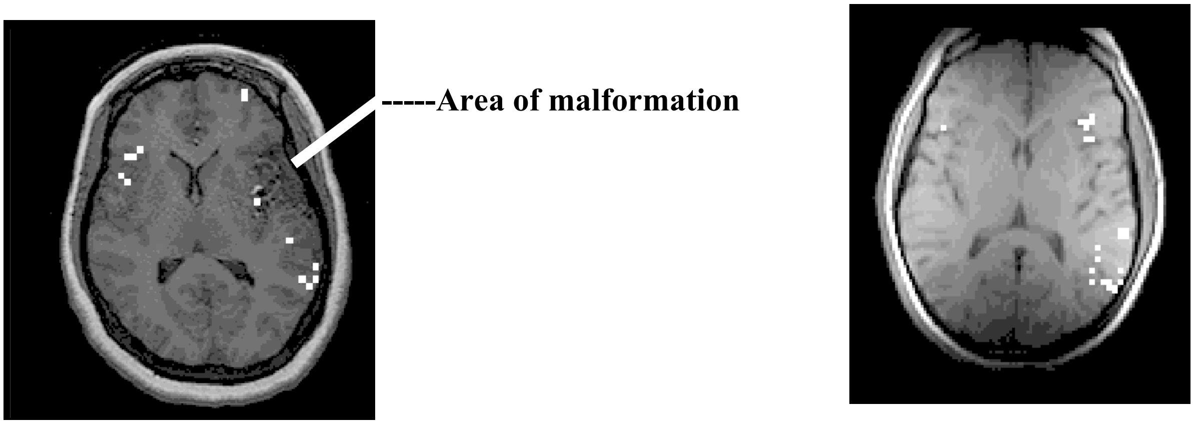


Figure 10. The activation results for the patient with the AVM (visible as a large darkened area in the left frontal region), along with the comparable data from a normal college student, both performing a language comprehension task. For the college student, the two activated cortical areas (superior/middle temporal gyrus and inferior frontal gyrus) are both largely left lateralized. For the patient with an AVM, the activation is cross-lateralized.

More recently, we applied a similar paradigm in a 45 year-old patient studied acutely and as he was recovering from stroke (Thulborn, Carpenter, & Just, in press). His structural lesion was approximately in a similar left frontal area. He presented with a dense expressive aphasia at time of stroke, which resolved into a mild anomia by 6 months. The fMRI in sentence comprehension was done at 3 days and again at 6 months post onset. We observed spontaneous changes in brain function in the months after stroke-induced aphasia. Specifically, there was a rightward shift of language-related brain activation to right hemisphere homologues of damaged and undamaged areas. In other words, there was a readjustment of the functional network that was adaptive to the physical damage during a period of recovery of language comprehension.

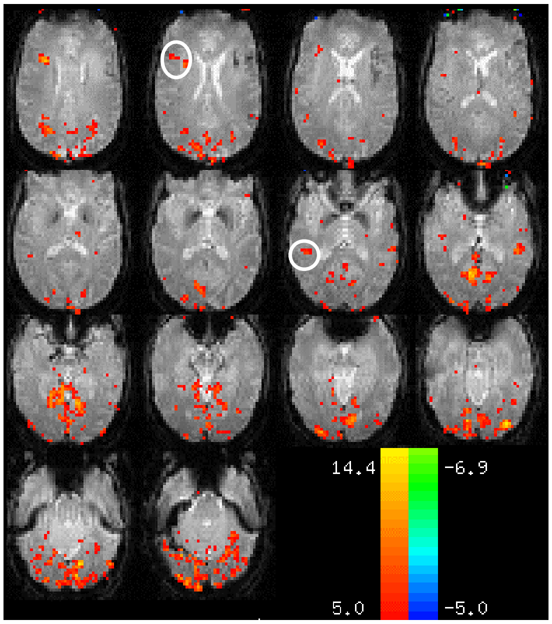


Figure 11. The activation results in the sentence reading task for a patient 6 months post stroke onset, after considerable spontaneous language recovery. The pattern suggests a rightward shift of language-related brain activation to right hemisphere homologues of damaged and undamaged areas. This shift is shown here by the circles around some of the activation in the right homologue of Broca's and Wernicke's areas. (Adapted from "Plasticity of language-related brain function during recovery from stroke" by Thulborn, Carpenter, & Just, *Stroke,* in press.)

The final pattern of activation during sentence comprehension is somewhat similar for the stroke patient and the AVM patients, although they came to be in this state through routes that occurred at very different times of their lives. We can speculate that in the AVM patient, the AVM may have preceded the development of the language function in childhood, and that the resulting cross-lateralization reflects the plasticity of brain function during early childhood. The network adaptivity seems similar despite the differences in age of onset.

## The Cortical Systems Underlying Visuo-spatial Processing

The principles that we have described in the context of the cortical system for language comprehension apply equally to the visuo-spatial processing system. The spatial processing participates in various rigid and non-rigid spatial transformations that are evoked when reasoning about objects in space, as for example, when a neuro-radiologist imagines how a series of two dimensional MR images might be mentally combined and mapped onto a three dimensional brain. Numerous behavioral studies have suggested that in young adults, the systems supporting language comprehension and visuospatial reasoning are somewhat separable (Carroll, 1993; Jurden, 1995; Shah & Miyake, 1996), and so it is perhaps not surprising that there is some partial dissociation cortically as well.

The cortical system supporting visuo-spatial processing has several specialized subsystems, but we focus on two main pathways that originate in the primary visual area and then project forward with extensive connections in the visual processing areas, including V2, V4 and V5. One pathway, the ventral stream, feeds into the inferior temporal lobe and is largely specialized for object recognition (Farah, 1990; Ungerleider & Haxby, 1994). The second subsystem, the dorsal stream, connects to the parietal lobe and is involved in spatial analysis and processing (Ungerleider & Mishkin, 1982; Ungerleider & Haxby, 1994). A third focus of interest includes the motor systems that compute eye movements in response to internal switches of attention, and which includes the precentral gyrus and the posterior middle frontal gyrus, and other cortical areas around and along the interhemispheric fissure.

These regions are co-activated in the visuo-spatial task of mental rotation. In this paradigm, a participant judges whether two pictures depict either the same object (but possibly at different orientations), as illustrated by the top pair of three-dimensional cube figures in the top of Figure 12 (Arnoult, 1954; Shepard & Metzler, 1971). On some trials, the participant is shown two mirror image isomers, as in the middle row of Figure 12. Participants report that they imagine one figure rotating into the orientation of the other figure; consistent with these self reports, the average decision time increases monotonically with the angular disparity between two pictures of the same object (Shepard & Metzler, 1971). The underlying cognitive processes involve mentally representing the objects, imaging part of one of them at successive orientations that close the distance between the objects' orientations, and then evaluating whether the rest of the object lines up with the target object (Just & Carpenter, 1976)

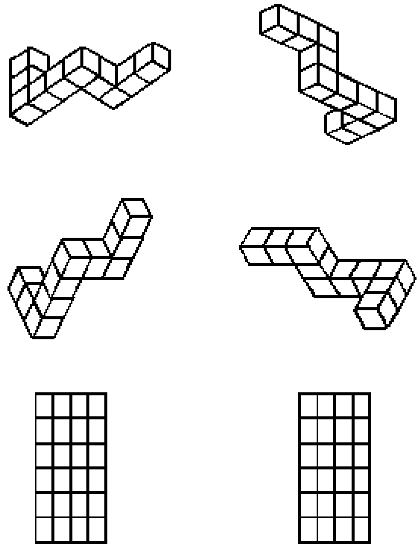


Figure 12. Stimuli from a mental rotation task, adapted from Shepard and Metzler (1971). The participant must judge whether a pair of figures, such as the ones at the top or those in the middle, represent the same object or mirror image isomers. The bottom shows two grids that participants were asked to scan, square by square, to compare the activation associated with eye fixations to that associated with mental rotation. (From "Graded functional activation in the visuo-spatial system with the amount of task demand" by Carpenter, Just, Keller, Eddy, & Thulborn, 1999, *Journal of Cognitive Neuroscience*, Figure 1, p.10. Copyright 1999 by the MIT Press. Reprinted with permission).

Earlier neuroimaging studies showed activation in the parietal region during mental rotation (Cohen et al., 1996; Alivisatos & Petrides, 1997), supporting the hypothesis derived from single-cell studies that this cortical region is partially involved in computing visuo-spatial coordinates at successive orientations. Based on the resource demand perspective, we hypothesized that there should be an increase in fMRI-measured activation in the parietal regions as a function of the amount of mental rotation (Carpenter, Just, Keller, Eddy & Thulborn, 1999a). The experimental conditions involved a graded manipulation of the angular disparity between the two figures, either 0°, 40°, 80° or 120°, along with a baseline fixation condition. Based on a computational model of the task, we predicted a monotonic increase in parietal activation as a function of the increase in angular disparity. Specifically, larger angular disparities require more resources for both computing more intermediate orientations and for maintaining representations of both stimuli being compared. Finally, to contrast task demand with simply task duration, we included a condition in which participants visually scanned a fixed grid to assess the impact of multiple eye fixations in the absence of rotation, as shown in the bottom row of Figure 12. The grid-scanning task was designed to take longer than the rotation conditions, but in spite of this, it was predicted that it should result in less activation than the rotation task because it involved very little computation.

An initial study, using a 1.5 Tesla GE scanner and 7-9 coronal slices, focused almost exclusively on activation in the parietal region. The second study used the same paradigm with a 3.0T scanner and 14 slices in an axial orientation, which enabled us to quantify the activation in more cortical regions, including most of the inferior temporal region and the frontal regions. These two studies, using the identical task paradigm, permit the evaluation of the effect of field strength on the results.

Figure 13 shows the positions of three slices that illustrate the type of data we obtained. The indicated superior slice shows some of the activation associated with the attentional and motor systems. The medial slice shows activation around the intraparietal sulcus associated primarily with the visuo-spatial computations, and the indicated more inferior slice shows the activation associated with the inferior temporal regions. In Figure 14, structural images of these three slices constitute the rows. Superimposed on the structural images is the average activation in each of the five conditions, the four rotation conditions (0°, 40°, 80°, and 120°) and the grid condition, for a typical participant. The white areas indicate the voxels that were activated significantly above the baseline fixation condition. The first row in

Figure 14 (slice 2 from the top in Figure 13) is through the centrum semiovale. The activation is in the area of the precentral sulcus (the frontal eye fields) and along the cortex of the interhemispheric fissure (supplementary eye field), and it tends to be high and similar in the grid and four rotation conditions. The second row, through the cingulate gyrus, shows activation in the intraparietal sulcus and gyri. The number of activated voxels is relatively low in the grid condition and much higher in the rotation conditions, where it tends to increase with angular disparity. The third row, through the inferior temporal-occipital lobes, shows activation to be high in the rotation conditions and lower in the grid condition. This general description of the results was supported by the analyses of multi-slice ROI's across the participants.

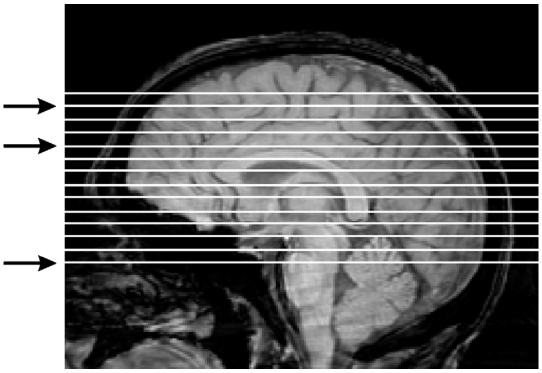


Figure 13. The positions of three slices in a sagittal scout to illustrate the data obtained from three main regions of interest for one participant. The top arrow indicates a slice includes areas associated with the attentional and motor systems. The middle arrow indicates a slice that includes regions around the intraparietal sulcus, regions associated primarily with the visuo-spatial computations. The more inferior slice includes the inferior temporal regions that are more associated with pattern recognition (From "Graded functional activation in the visuo-spatial system with the amount of task demand" by Carpenter, Just, Keller, Eddy, & Thulborn, 1999, *Journal of Cognitive Neuroscience*, Figure 3, p. 13. Copyright 1999 by the MIT Press. Reprinted with permission).

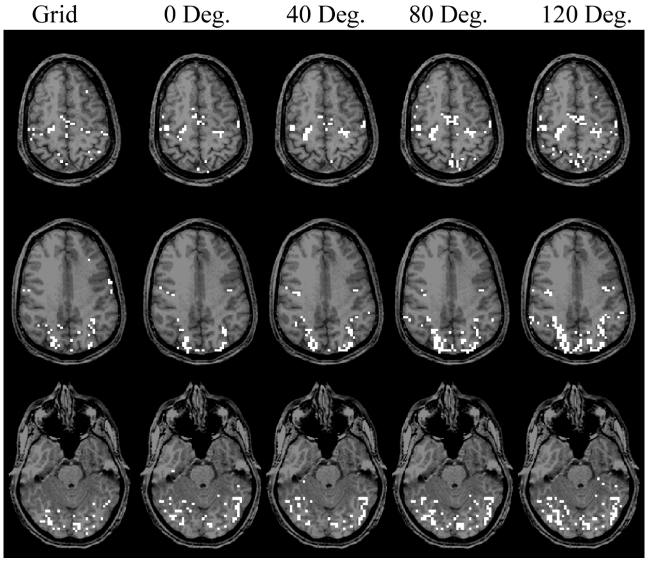


Figure 14. Statistical probability maps superimposed on structural images for the four rotation conditions and the grid conditions for the three slices indicated in Figure 13. The white voxels were activated significantly above the baseline fixation condition. The first row (top arrow in Figure 13) is through the centrum semiovale. The activation is in the area of the precentral sulcus (the frontal eye fields) and along the cortex of the interhemispheric fissure (supplementary eye field), and it tends to be high and similar in the grid and four rotation conditions. The second row, through the cingulate gyrus, shows activation in the intraparietal sulcus and gyri. The number of activated voxels is relatively low in the grid condition and much higher in the rotation conditions, where it tends to increase with angular disparity. The third row, through the inferior temporal-occipital lobes, shows activation to be high in the rotation conditions and lower in the grid condition. (From "Graded functional activation in the visuo-spatial system with the amount of task demand" by Carpenter, Just, Keller, Eddy, & Thulborn, 1999, *Journal of Cognitive Neuroscience*, Figure 4, p. 14. Copyright 1999 by the MIT Press. Reprinted with permission).

The major prediction concerned the effect of rotation on activation in the parietal region, specifically whether larger angular disparities, which consume more activation resources in the computational model, are associated with increased fMRI-measured activation. As Figure 15 indicates, the number of significantly activated voxels in the parietal region, most of which were in and around the region of the intraparietal sulcus and into the transverse occipital sulcus, increased monotonically with angular disparity. These data demonstrate two important properties. First, the linear trend shows the quantitative impact of the amount of a particular type of task demand on activation as assessed with fMRI, which constitutes major support for the approach. Second, the bilaterality of the effects indicates the involvement of both hemispheres in this visuo-spatial task, in contrast to the rather strong laterality of many language comprehension tasks. The bilaterality is most asymmetric at 0°, where the right hemisphere is noticeably more responsive than the left, suggesting that bilaterality may increase with the task's demand, as it does in language processing. The right-hand side of Figure 15 indicates that the increased demand associated with more mental rotation also led to an increase in the average percentage of activation increase over the baseline fixation condition. Thus, as with the sentence comprehension, the cortical systems subserving visuo-spatial imaging show increased activation with demand.

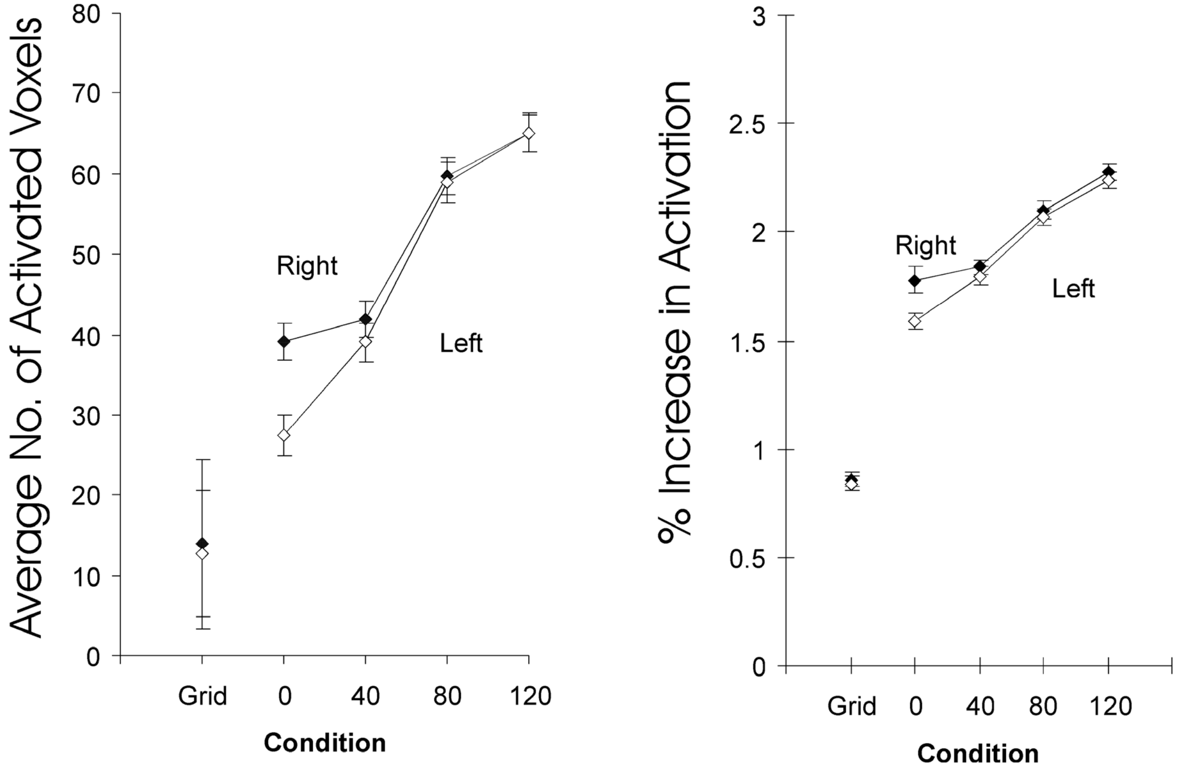


Figure 15. The average number of activated voxels (left hand side) and the average percentage of activation (right hand side) in the parietal regions of 7 subjects both increase monotonically with the amount of mental rotation, and both measures are higher than for the grid condition. These data were acquired with a 3.0T scanner. (From "Graded functional activation in the visuo-spatial system with the amount of task demand" by Carpenter, Just, Keller, Eddy, & Thulborn, 1999, *Journal of Cognitive Neuroscience*, Figure 5, p. 15. Copyright 1999 by the MIT Press. Reprinted with permission).

Compared to the 3.0T results, the 1.5T study showed the same quantitative trends, but a much lower number of voxels that were significantly activated. Figure 16 shows a monotonic increase in the number of voxels significantly activated above baseline in the parietal regions for the 1.5T study, which involved the same paradigm and approximately the same number of subjects. This difference is consistent with the higher signal-to-noise ratio (by a factor of two [Thulborn et al., 1996]) and with the higher sensitivity for magnetic susceptibility effects of the 3.0T compared to the 1.5T systems. In fact, the increased susceptibility of the 3.0T (approaching a quadratic power [Thulborn et al., 1982]) increases the sensitivity to the microvasculature that biases toward the smaller vessels. Both the higher signal-to-noise ratio and increased sensitivity would enable one to detect smaller increases in activation, which would increase the number of voxels that would be found to be significantly activated.

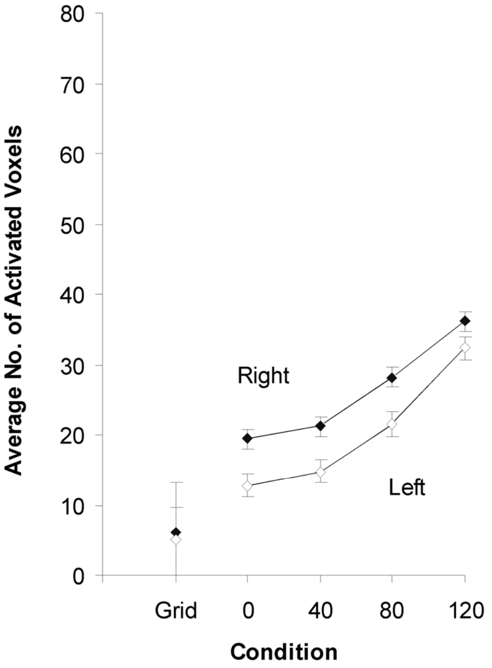


Figure 16. The average number of activated voxels in the parietal regions increases monotonically with the amount of mental rotation. These data, acquired with a 1.5T scanner, show less of an effect than the data acquired with a 3.0T scanner, shown in Figure 17. (Adapted from “Graded functional activation in the visuo-spatial system with the amount of task demand” by Carpenter, Just, Keller, Eddy, & Thulborn, 1999, *Journal of Cognitive Neuroscience*, Figure 6, p. 15).

As expected, the increase in demand not only affected the activation in the parietal region, but also in the inferior temporal region, a region that is primarily (but not exclusively) involved in object recognition. The results, averaged across participants, are shown in Figure 17 for the 3.0T study. The figure indicates a considerable elevation in the number of activated voxels and the amplitude of activation in all four of the rotation conditions, particularly compared to the grid scanning condition. The increase is not monotonic, indicating that the computations in this region are more uniform throughout the rotation task. What the high activation in this region along with the activation in the parietal regions indicates is that the mental rotation task emerges from an interaction among systems that scale different regions and hemispheres.

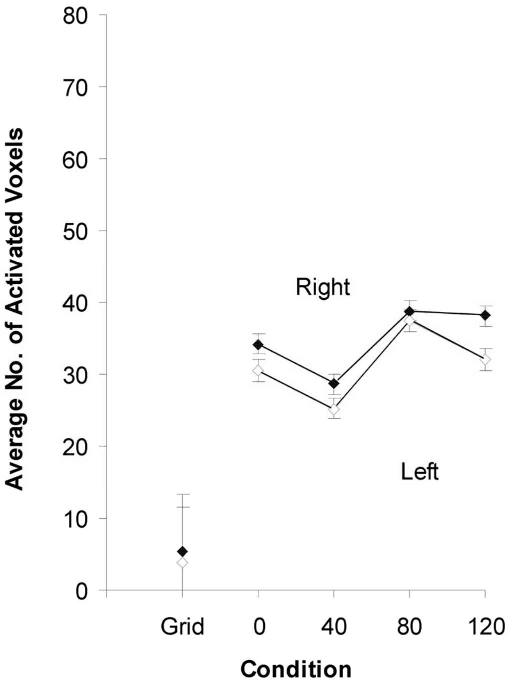


Figure 17. The average number of activated voxels in the inferior temporal regions is elevated for the rotation conditions compared to the grid scanning conditions, although the increase is not monotonic. These data were acquired with a 3.0T scanner. (Adapted from “Graded functional activation in the visuo-spatial system with the amount of task demand” by

Carpenter, Just, Keller, Eddy, & Thulborn, 1999, *Journal of Cognitive Neuroscience*, Figure 7, p. 17).

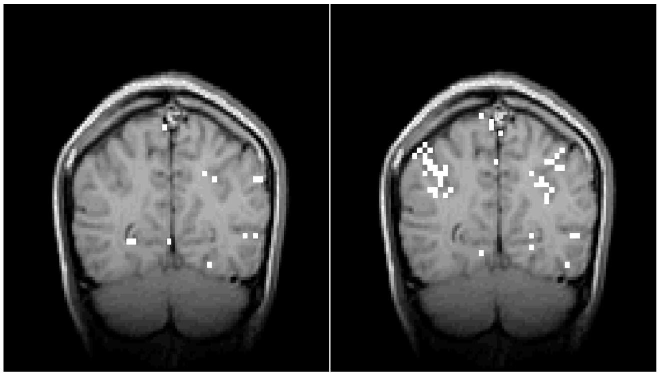
### Communication between linguistic and visuo-spatial network.

The language and visuo-spatial networks, which appear to be cortically segregated across the previous studies we have reviewed, also directly communicate with each other. Such communication suggests that the modularity of various large-scale cortical networks is only one of degree, and therefore, the cognitive systems and the cortical neural systems that support them may more appropriately be characterized by degrees of interaction. We examined the interaction between the language and visuo-spatial systems by monitoring the time course of activation in the key cortical regions associated with each system while a participant read a sentence that referred to a spatial configuration. The task involves reading a sentence, such as *It is (isn't) true that the star is above the plus,* and then verifying it against a picture, such as a star above a plus (Just, Carpenter, Keller, Eddy & Thulborn, 1996; Carpenter, Just, Keller, Eddy & Thulborn, 1999b). Moreover, the study used an event-related method to examine the time course of activation at various points during the sentence processing phase and the picture-processing phase, rather than relying on asymptotic activation that sums across different phases of the task. The study manipulated the difficulty of the comprehension task by comparing the comprehension of negative sentences to that for their affirmative counterparts. Numerous behavioral studies have indicated that negative sentences are more difficult to process than affirmatives, resulting in increased reading time and errors (Chase & Clark, 1972; Carpenter & Just, 1975). This complexity leads to the prediction of higher levels of activation during the processing of negative sentences than affirmative sentences in the left posterior superior temporal region, which we have shown is associated with language processing. The study also examined the activation in the parietal regions because of their association with various visuo-spatial processes, such as mental rotation and covert spatial attention (Carpenter, Just, Keller, Eddy, & Thulborn, 1999a; Alivisatos & Petrides, 1997; Cohen et al., 1996; Lynch, Mountcastle, Talbo, & Yin, 1977; Tagaris et al., 1997). The reason for examining activation in the parietal regions is that during sentence reading, the participant is preparing to compare the linguistic representation to a picture. If the neural processing of language is not encapsulated but also involves some contact with the system representing the sentence's referent, then there might also be activation in the regions associated with visuo-spatial relations. Such an effect (which describes the obtained results) is consistent with the hypothesis that language processing is not restricted to the classically associated cortical regions. The co-activation in two regions argues against the view that the processing in the linguistic region is temporally isolated from processing in other cortical regions.

A typical trial involved a sentence (such as, *It isn't true that the star is above the plus)*, that was either affirmative or negative, followed by a picture of a star and a plus accompanied by a diagrammatic instruction to mentally rotate the array by $0^o$ or $135^o$ before comparing it to the sentence. These two conditions (affirmative versus negative sentence and $0^o$ or $135^o$ rotation) were varied orthogonally to manipulate the cognitive demand in each stage. To allow the activation to return to baseline between trials, a 20 s fixation epoch occurred between each trial, and the activation during the last 14 s averaged across trials constituted the baseline. Imaging was performed at 1.5T using gradient-echo EPI (Acquisition parameters were 7 coronal slices, TR=1500 ms, TE= 50ms, flip angle=$90^o$, 128 x 64 acquisition matrix, FOV = x $cm^2$, 5 mm slice thickness, 1mm gap).

To monitor the time course of activation, the sentence presentation and the picture presentation were synchronized electronically with the scanner. The TR of 1500 ms with 7 coronal slices allowed frequent sampling of the two main cortical regions of interest. A total of 5 slices defined the posterior temporal regions, and they were acquired with a mean elapsed time of 940 ms for the first acquisition interval, 2440 ms for the second, and so forth. For the 5 slices that defined the parietal regions, the corresponding mean elapsed time was 850 ms and 2350 ms for the first and second acquisition intervals, and so forth. The voxels of interest were identified by first computing separate voxel-wise t-statistics that compared the activation for the affirmative condition and negative condition to the baseline activation during the sentence presentation using a threshold of $\underline{t} \geq 4.5$.

Figure 18 shows two immediately successive brain states for one participant, the first acquired over approximately 3.5 s of sentence processing, the second over about 4 s of picture inspection, rotation, and comparison. Initially, during sentence reading, there is significant activation in the left temporal area. There is also some activation in the parietal regions, although the onset is slower. In both regions, the activation during the sentence processing is greater for the negative sentences than for the affirmative sentences. Then during picture inspection, there is considerably more activation in the parietal regions, most of which was in and around the intraparietal sulcus (as illustrated in the Figure). These two images constitute a two-frame brain image "movie" of sequential thought processes, showing the brain activation primarily first in one region and then primarily in another, as the nature of the cognitive activity changes.



Sentence Reading Picture Inspection

Figure 18. Two immediately successive brain states for one participant, the first acquired over approximately 3.5 s of sentence processing, the second over about 4 s of picture inspection, rotation, and comparison. Initially, during sentence reading phase, there is significant activation in the left temporal area and some activation in the parietal regions. During the subsequent picture inspection phase, there is considerably more activation in the parietal regions, much of which is in and around the intraparietal sulcus (From "Movies of the brain: Imaging a sequence of cognitive processes" by Just, Carpenter, Keller, & Thulborn, 1996, *NeuroImage, 3*, S250. Copyright 1996 by Academic Press. Reprinted with permission).

This asymptotic picture of how the activation shifts does not convey an important feature of the activation dynamics. Namely, even during the sentence comprehension phase, the activation in both the left posterior temporal region and the parietal regions was significantly above the baseline. Figure 19 shows the time course of the activation in the left posterior temporal region (the left panel) and the left parietal region (the right panel) during the sentence comprehension phase. Note that even when the participants were just beginning to read the sentence, there was significant activation in the parietal region. Moreover, in both regions, the activation was greater for negative than affirmative conditions, indicating that the impact of linguistic difficulty extends to regions that process the spatial information to which the sentences referred. Thus, the dynamics are more subtle than simply an on-off switch associated with each major processing stage. Rather, the co-activation of these regions suggests a more continuous cascade of activation among communicating cortical regions. The co-activation suggests that these component systems, such as the linguistic comprehension system and the visuo-spatial system, are only somewhat independent and, depending on the task, can also work together in a closely coupled way.

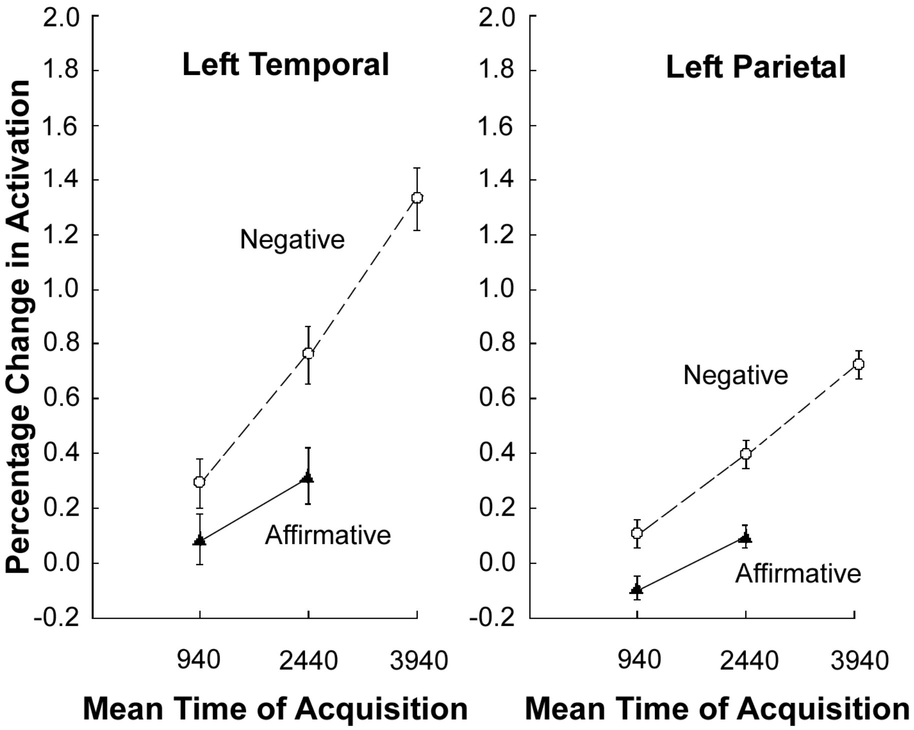


Figure 19. The time course of activation in the left posterior temporal region (the left panel) and the left parietal region (the right panel) during sentence reading for each of several acquisition images. Both regions show significant activation above baseline, and the activation is greater for negative than affirmative sentences, suggesting that sentence processing affects the visuo-spatial network in the parietal region while the sentence is still being comprehended.

## The Capacity Utilization Model

Cognitive computations are neurally instantiated through a complex biochemical process that can be seen as a form of energy transformation. Like any biological energy process, this transformation requires resources. Moreover, the demand for and consumption of resources at the neural level can be abstractly mapped onto resource consumption in computational models of cognitive processes. From this perspective, the fundamental resource assumption of the current theory is that immediate thought is supported by a set of limited, system-specific resources that enable the maintenance of representations and the cognitive operations themselves. Fortunately for functional neuroimaging, brain activation reflects at least one aspect of the resource consumption engendered by the cognitive activity. At a macro-level, the entire cognitive system is composed of several major systems, each of which is supported by its own resource pool. For example, the cortical neural systems corresponding to the language and spatial systems consist of several anatomically distinct and somewhat separated subsystems. For example, language is partially subserved by cortical regions in the frontal and in the temporal lobes, more actively so in the left hemisphere, but also in the right. Each subsystem may be further decomposable, at several temporal grains (in the computational model) and several temporal and spatial grains (in various neuroimaging data sets).

Within a system, such as the language processing system, demand on the resources arises in part from keeping the activation level of a representational element above some pre-specified threshold and processing. The computations that are performed by the cognitive system are dependent on the same resource pool that is drawn on to maintain the activation of representational elements. The computations are accomplished by activation-manipulating production rules (if-then rules or condition-action contingencies). If the condition elements of a rule have an adequately high activation level, the rule performs its function by propagating activation to its action elements. A parsing production rule, for example, might have as its condition the encoding of a definite article (*the*) and as its action, increasing the activation associated with the representation of a noun phrase.

The supply of the activation resources in the system is limited. If the productions require a large amount of activation to complete their functions, for example, if there are many elements to keep active and difficult computations to complete, then the demands on the resource pool may begin to outstrip the supply. In that case, when a production fires it will propagate less activation than it would otherwise. Its propagation of activation is scaled back in proportion to the amount of activation shortage. This slows the processing rate by requiring the production to fire over more cycles to activate its target to a given level. Activation also may be conserved by de-allocating some of the activation associated with previously activated elements, producing gradual forgetting.

Furthermore, the size of the supply of resources for a system is assumed to vary among normal individuals and to be a source of individual differences in cognitive performance. Concretely, the neural resources is a broad category that includes neurotransmitters' functioning, the various metabolic systems supporting the neural system, and also the structural connectivity or integrity of the neural systems, drawing directly from the concept of neural-systems efficiency (Parks et al., 1989). In the functional analysis, these can be abstractly mapped onto the aggregate concept of functional resources that enable various cognitive computations. While the theory provides a framework for considering individual differences, it does not account for the origin of such differences, which presumably arise from an interaction of biological and environmental factors (such as experience and training). In addition, pathological neurological changes in an adult, such as those associated with strokes (Thulborn, Carpenter & Just, in press) or dementia (Thulborn, Martin, Sweeney, 1998), may be viewed as reducing the resource supply.

**Defining capacity utilization.**

Within this framework, the amount of demand that a task imposes on a resource pool can be defined as the number of units of activation required over a given time interval to perform the task. This quantity can be measured in the course of the model's performance of the task. This framework provides a concrete operationalization of capacity utilization, a concept that was originally proposed in economics and refers to the *proportion* of resources that a system uses in a given time interval. For example, if a manufacturing plant operates for 8 hours one day but is capable of operating a maximum of 24 hours per day, then the capacity utilization is 33% for that day. Analogously, if an individual needs 15 units of activation to perform a cognitive task and has a total of 60 units of activation available, the capacity utilization for the task is 25%. Capacity utilization, thus, is conjointly determined both by the amount of resources required by the task (i.e., demand) and the amount of resources available (i.e., supply). For a given person, the more demanding the task is, the more activation should be observed, provided the task difficulty remains performable. This outcome was observed in the sentence comprehension and mental rotation studies described elsewhere in this article. For a given level of task difficulty (i.e. keeping the demand constant), the smaller the resource supply is across a range of individuals (due to lower skill level, brain damage, or some biological factor), the greater should be the amount of activation. This result has been obtained in several studies, one of which observed a high negative correlation between the amount of brain activation during the performance of visual analogies (from an intelligence test called the Raven Progressive Matrices Test) and the test score (Haier, 1993).

That is, the lower the test score, the greater the amount of observed activation.

The construct of capacity utilization focuses on a dimension that has been difficult to measure and that is often neglected in cognitive theory in spite of its importance: a characterization of how hard a cognitive system has to work to perform a given task (Just, Carpenter, Keller, Eddy & Thulborn, 1996). It seems introspectively obvious that our minds work much harder at some times than at other times. This notion of the mind's "working harder" is concretized in the model, which provides mechanisms for mapping from processing characteristics to capacity utilization as well as to response times and error rates.

**Computational mechanisms.**

Besides these assumptions about the resources, the theory also proposes a particular cognitive architecture that we will briefly describe. The architecture is a hybrid with both symbolic and connectionist features. The connectionist mechanisms have to do with the activation-based processing and storage, that gives each function a graded quality. The symbolic mechanisms consist of condition-action rules that express procedural knowledge. As the activation of elements in a condition side of a rule reaches a threshold, the production increments the activation of the action elements. The processing is graded in the sense that production rules fire reiteratively, usually until they attain their goal. Thus, conditions and actions are linked by productions that propagate activation to action elements. The productions are like dynamically formed links between nodes in a connectionist network (Just, Carpenter, & Varma, 1999). The condition-action rules permit an organization of high level processing (relating high level goals and the actions required to attain them, as in problem solving) as well as lower-level associative processing. The production rules self-schedule themselves based on the emergence of their enabling conditions, without any central control mechanism (such as a central executive). Furthermore, the processing can be parallel, in that all satisfied productions can fire in parallel in a given cycle if resources permit it, or processing can be serial, if the initiation of some production is dependent on the activation of a product of some preceding computation.

The theory focuses on capacity utilization at a particular system level that aggregates over lower-levels processes that undoubtedly exist and may even set parameters on the efficiency of processes at the higher-level. For example, the activation to threshold of a particular set of representations likely entails the inhibition of competing representations, although that is not yet incorporated into the modeling or in this mapping. Nevertheless, the architecture reflects a beginning theoretical effort to focus on the dynamics of resource modulation during immediate thought.

A new version of the modeling system, tentatively called 4CAPS, is currently under development. Its main innovation is that 4CAPS contains a number of embedded production systems which correspond to large-scale cortical neural networks. Each embedded production system has its own time scale and its own set of ordered preferences of processing style, but the principles of operation are common across the subsystems. The goal is to simulate not only the content, time course, and errorfulness of human performance in various high level cognitive tasks, but also the relative amount of neural activation that the task engenders in each of several neural components/subsystems of cognition.

**Clinical applications take capacity utilization into account**.

The pragmatic implication is that in the fMRI testing of any clinical case, it is important to meet a set of conditions. First, the patient must be effectively performing the cognitive task, as assessed by concurrent behavioral measures, such as response accuracy. There is usually a range of task difficulty levels that a given patient can effectively perform, defining a dynamic range of that person's system for that type of task. If the task is too difficult to perform (such that the response accuracy approaches chance level), then the amount of brain activation decreases relative to easier, performable levels of the task. Such decreases are not paradoxical non-monotonicities in the effect of cognitive workload, but simply reflect a kind of "giving up" on the task, and hence display a decrease in brain activation. A second important condition is that the task should probe several points along the dynamic range of the tested system, extracting the counterpart of a dose-response curve. Tasks that are so easy that they do not adequately engage the system may fail to reveal higher-level dysfunctions. For example, to test "language" ability in patients, single-word identification or word-reading tasks are sometimes used. In the case of high-functioning individuals with autism, there is no deficit whatsoever compared to control subjects in the ability to process single words (Minshew, Goldstein & Siegel, 1997). In fact, the high-functioning individuals with autism generally perform better than the matched controls on these tasks. However, when the same two groups are compared in a complex sentence comprehension task, then deficits can be found in the autistic patients. Any fMRI comparison of other patient groups should similarly examine brain function at several levels of difficulty, to ensure that there is no resource deficit that might be observable only at difficult (yet still performable) levels of the task.

### Localization of function.

Many researchers consider functional neuroimaging to be a localization tool, to associate psychological function with locations of brain activation. However, the issue of localization is more complex and more interesting than this first-order research suggests. First, for every psychological function that is executed, multiple brain areas activate. Second, the mapping should be from psychological function to a pattern of brain activation, not to a set of locations. To be sure, the pattern must apply to a set of locations, but ultimately, a psychological function will not map to a single location or to a single neuron. Finally, brain-imaging findings indicate that the mapping between psychological function and brain activation is dynamic, such that the size of the location and number of locations activated changes with the amount of computational demand. The computational demands themselves are dynamic, changing over a short time period within the task and over a longer time period, with factors such as learning, fatigue, and so forth.

The classical view of localization attempts to associate each cortical region with a single cognitive process. Such a view leads to the phrenological models of the brain, updated to include more cognitive functions in place of personality attributes, but essentially proposing a one-to-one map of structure to function. A relatively recent version of this approach to describing cortical function is depicted in Figure 20. Implicitly, this view often assumes that the processing from one stage to the next is serial and sequential, without room for feedback. For example, the Wernicke-Geschwind model of word reading and pronunciation, shown in Figure 20, proposed that written words are first decoded in the visual areas, then the representation was transmitted to the posterior temporal region for interpretation, and then onto the frontal region for translation into a spoken code that was translated into the motor output. With this view, the activation of multiple regions simply reflects the view that cognitive tasks are complex and involve multiple basic cognitive processes.

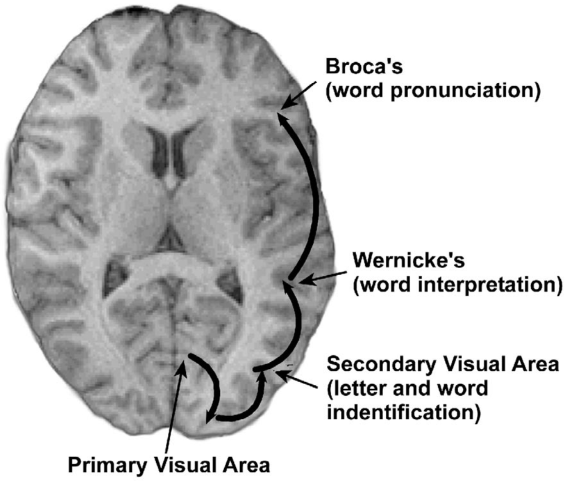


Figure 20. A depiction of a one-to-one mapping that is conventionally postulated between cognitive processes and brain areas. Each process is associated with a single brain region, and regions are assumed to serially process information from input to output, as indicated by the curved black arrows. For example, the Geschwind-Wernicke model proposed that in order to pronounce a printed word, it was first encoded in the visual areas, then interpreted in Wernicke's area, and then translated into a pronounceable code in Broca's area. The

alternative view, schematically depicted in Figure 1 and supported by the very high field studies described in this article, suggests that there is a many-to-many mapping between cognitive computations and cortical regions.

The alternative perspective that has been examined in the reported research is that the mapping between function and cortical area is not one-to-one, but one-to-many. That is, a cognitive computation is subserved by more than one region, and moreover, a region may participate in multiple computations, although with different weights. Moreover, the connections among regions are not simply one way; the studies reported here and elsewhere suggest that cognition is supported by systems that are linked by extensive feedback as well as feedforward connections. One immediate implication is that brain damage impairs the function of not just the lesioned area, but of all the networks which include the damaged area. As a result, the emerging map between cognitive function and neural region is much more complex, highly interactive and non-localized, as the sketch in Figure 1 begins to depict.

**Functional connectivity**.

Referring to a large-scale network implies that there is a considerable degree of interaction among the network components. The network is identified in the first place by the co-activation of its members. Neuroimaging provides several types of further evidence of interaction, beyond co-activation. First, brain activation can reveal co-modulation of two or more network components by the same independent variable. For example, variation in the syntactic complexity of sentences similarly affects Broca's and Wernicke's areas, suggesting that they might be interacting. Second, the precise time course of the activation can be compared, to reveal similarities in activation time course across disparate areas of the brain. If there is a cluster of voxels defined by having similar time courses, and that cluster is distributed over two or more components of the network, then it is likely that the participating voxels in those components are interacting. New statistical methods and software tools (such as Evident) are being developed to cluster voxels based on the similarity of the time course of their activation. The methods identify network members on the basis of not just coactivation, but on coactivation with the same time course. This general approach for identifying network coordination has been called *functional connectivity* (Horwitz, 1998).

We have begun such functional connectivity analysis in some sentence comprehension studies. The data are analyzed by finding the voxels whose activations are time-locked to each other and grouping all the voxels with a similar time course irrespective of their location. It is possible to identify a single cluster of voxels that corresponds to the entire set of activated voxels in the t-map or statistical probability map of the type shown throughout this chapter. However, if we further refine the clustering, it is possible to further subdivide the entire group of activated voxels into subgroups that constitute functional sub-networks. The identified sub-networks are very meaningful. The result for one participant in a 3.0T language study, in Figure 20, shows the early promise of this approach, identifying a sub-network that includes a subset of the voxels in Wernicke's area to those in the left prefrontal cortex.

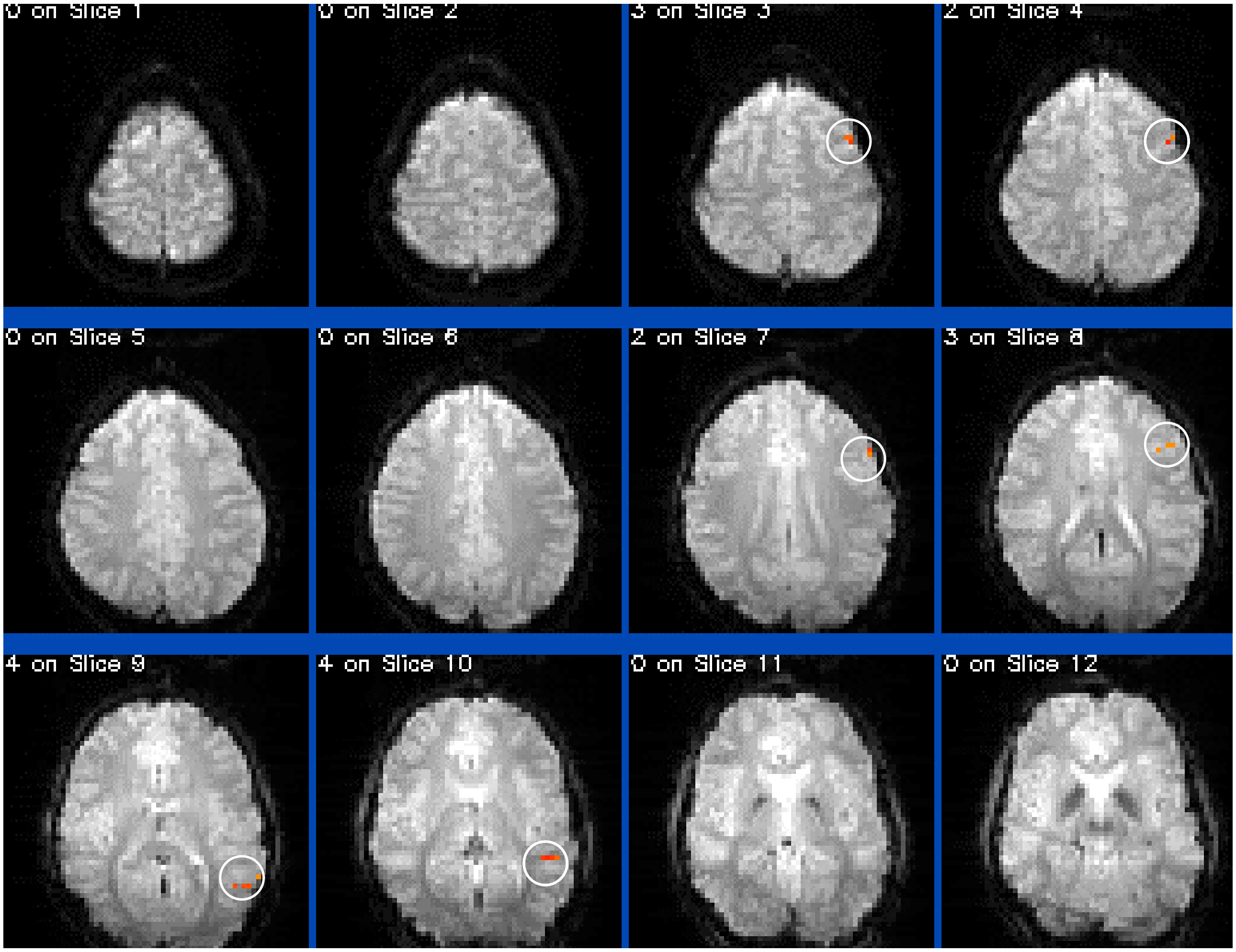


Figure 21. A sub-network extracted for one participant in a 3.0T language study, shows a subset of voxels in Wernicke's area and the left prefrontal cortex (indicated by circles). These voxels share a similar time course of activation throughout the language comprehension paradigm, suggesting that they are functionally connected.

## Information from brain imaging about cognition.

All imaging reveals some spatial pattern, and fMRI is no different at a general level. However, the interpretation of fMRI provides considerable additional information. fMRI reveals the location of activated parts of the brain, and more importantly, it reveals the co-activation of cortical components in a network. With the help of time-series-based clustering techniques, it can also reveal functional connectivity in the network. Additionally, fMRI reveals the amount of activation in each network component in a particular task condition, reflecting conjointly the distribution of computational demands imposed by the task and the distribution of neural (biological and cognitive) resources brought to bear by the subject's brain. fMRI can also reveal the time course of brain activation, within the temporal limits of resolution imposed by the T1 relaxation times (on the order of 1 sec). fMRI also reveals how a damaged network responds after adaptation, providing ample clinical application of the technique. But the fundamental conceptual insights fostered by fMRI technology in combination with developing theories of cognitive function illuminate the dynamic and interactive brain networks that subserve thinking and that constitute the mind.

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