COMMENTARY

Localization of Function All Over Again

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In this special issue of NeuroImage, five leading groups of investigators of human brain function have addressed a key issue of cerebral cortical functional organization, an issue that has been raised and settled in different ways at different times in the history of the brain sciences. The pendulum has swung from localization in the time of Gall and Spurzheim through Fritsch and Hitzig to equipotentiality in the time of Lashley. What is notable about the five sets of studies in this special issue is their focus on both localization issues in the prefrontal cortex and the interaction between noninvasive studies in humans and experimental research at the cellular level traditionally carried out in nonhuman primates. The cooperation between these fields is an extremely positive development providing stimulation and challenge for both fields. Studies in nonhuman primate models benefit from a testing ground for extrapolating findings and theories to the human condition. And conversely, cellular neurophysiology can provide an experimental testing ground for theories of human cognition based on patterns of areal activation under manipulated behavioral conditions. Indeed, the articles in this issue have been forthright about the limitations of fMRI with respect not only to the issue of spatial resolution but also to the sophistication of experimental and analytic procedures, particularly well explicated in the articles by Nystrom et al. and by Postle et al. in this volume. When the findings from both endeavors concur, science advances.

An excellent example of concordance between nonhuman primate and human studies is D'Esposito et al.'s adaptation of the experimental design of Quintana and Fuster (1992). Perhaps because the cognitive operations enforced in the monkey study were easily translated to humans, the results and conclusions of the human study turned out to be congruent not only with Quintana and Fuster but also with a large number of electrophysiological studies in nonhuman primates and also with cognitive and neuropsychological research in humans subjects. When imaging results in cognitive neuroscience can be bolstered by neurophysiological and/or anatomical results in nonhuman primates or in other mammals (e.g., psychopharmacological studies in rodents), cognitive neuroscience advances, and one has the sense of being on the right track and that pieces of the big puzzle might one day fit together. Importantly, confidence in the methodology of cognitive neuroscience is increased.

REVIVAL OF EQUIPOTENTIALITY?

On the other hand, when results between animal and human studies are not in full agreement, this discordance can be a catalyst for new ideas and approaches to difficult problems. The issue of functional specialization versus equipotential representation in the prefrontal cortex is a case in point. Studies in nonhuman primates have mapped areas of local specialization in the dorsal and the lateral prefrontal cortex (e.g., Goldman-Rakic, 1996a,b for recent review of this work). For example, neurons in areas 46 and 8A respond in a highly selective manner to the location of peripheral visual stimuli (Funahashi et al., 1989, 1990, 1991; Wilson et al., 1993; Chafee and Goldman-Rakic, 1998), whereas neurons in circumscribed patches on the inferior prefrontal convexity have been shown to respond selectively to pictures and objects presented at the center of the visual field (Wilson et al., 1994; O'Scalaidhe et al., 1997, 1999; Rao et al., 1997). Moreover, the segregation of information processing domains implied in single-cell recordings is in close accord with anatomical and behavioral studies in monkeys, with a considerable number of fMRI studies of object or spatial cognition, and with strong evidence from cognitive psychology that working memory is far from unitary but rather domain constrained (e.g., Baddeley, 1986; Miyake and Shah, 1999).

Four of the papers in the present special volume explicitly examine whether spatial cognition and object cognition in humans are anatomically and functionally dissociable. One group (Haxby et al., this volume) review work that has consistently observed evidence of areal segregation for object-based and space-based pro-
cesses, while the remaining three studies obtained a variety of negative results. As has recently been pointed out (Casey et al., 1998), there is good agreement in these studies, and in the field generally, that spatial processes activate regions of dorsolateral prefrontal and/or dorsal precentral areas. In this regard, considerable reproducibility exists across variations in hardware, statistical methods, and paradigms. The negative results arise from two sources: object-based tasks may also activate the same dorsolateral areas (Nystrom et al., this volume) or fail to activate ventral areas (e.g., Nystrom et al., Experiment 2). It seems reasonable to consider the possible sources of negative findings and discrepancies between imaging studies as represented by Haxby et al. vs the rest of the contribution and also between results in monkeys and in humans.

Some of the factors brought out in this volume include data analysis procedures, equation of task difficulty or memory load, and cognitive strategies such as cross-processing of stimuli by subjects, among others. For example, Nystrom et al. conducted two studies relevant to the spatial/nonspatial dichotomy. In order to equate the stimulus display in the spatial and nonspatial tasks in their Experiment 2, they displayed single letters in different locations in an n-back version of both a “location” and a “letters” working memory task. In accord with the specialization of a dorsal stream area for spatial processing, the location condition showed greater activation of a superior frontal sulcus locus (and several other dorsal stream loci) than the letters condition, which required recall of the letters themselves. The letters condition failed to selectively activate a ventral area on the inferior prefrontal convexity. Thus, no evidence for a double dissociation was observed. Two problems with this study, as the authors point out, are that the tasks were not equated for difficulty and that the letters task failed to activate Broca’s area in accord with prior studies of verbal memory. An additional factor that may have contributed to the overlap in dorsal areas includes the presentation of letters in random spatial locations, which coupled with the simplicity of the stimulus may have been permissive for attending to location plus letter (“blending”) as the authors aptly refer to it. Thus, by equating the stimuli in the two tasks, which would reasonably seem to be an obligatory design feature, the authors might have introduced Stroop-like interference from prepotent responses into both tasks, thus ensuring overlap in the activation profiles observed. The other study reported by Nystrom et al. (their Experiment 3) used shapes rather than letters as nonspatial stimuli in the nonspatial task, increasing its stimulus complexity and difficulty. Further, a word-reading task was introduced during the delay period in both conditions to preclude the use of verbal strategies in either task. With these changes, the main finding was higher signal in the right middle frontal gyrus in the spatial task and higher signal in the left inferior frontal gyrus for the shape task, including a portion of Broca’s area. This stronger experimental design produced results more in accord with a spatial/nonspatial specialization of function (which also tends to be realized as right/left hemisphere specialization). The activation of Broca’s area by a shape task in this study is one more piece of evidence that cognitive tasks are carried out at multiple levels of information processing (possible verbal mediation) despite the best efforts taken to isolate mental processes. Although the authors seemed reluctant to draw such a conclusion, the findings of Experiment 3 are quite consistent with expectations based on domain specificity and with a considerable number of previous findings in the literature, including their own (Casey et al., 1995, 1998), as well as with findings in the nonhuman primate.

One of the reservations expressed by Nystrom et al. concerns the changes attributable to load: load had a greater impact on signal intensity in dorsal areas than did location in Experiment 3. The summary given to their collective results was that “regions engaged by manipulations of working memory load are responsive to every type of stimulus information.” However, another explanation of this result may lie in a better understanding of the relationship between load and difficulty and whether increasing load also increases the engagement of multiple informational domains, i.e., “obligate encoding of multiple dimensions” in high load conditions. Still, taking the results of Experiment 3 at face value, the differential results accord with prior studies on spatial and/or nonspatial processing (Carlson et al., 1998; McCarthy et al., 1994; Baker et al., 1996; Smith et al., 1995, 1996; Courtney et al., 1996; Kelley et al., 1998; Wagner et al., 1998; Sweeney et al., 1996). Thus, of two studies designed to examine the segregation of spatial/nonspatial processing by areas in prefrontal cortex, one study was negative and the other positive. However, the negative study could be discounted because it did not meet acceptable standards of design by the author’s own analysis. It seems reasonable that the positive results can be claimed for segregation equally or more strongly than against it, especially as Nystrom et al. showed that equating for task difficulty and minimizing verbal mediation resulted in a completely different, and I would argue predictable, set of findings based on the literature.

The findings of a second group of three studies by Postle et al. were clearly not able to demonstrate functional localization. Postle et al. set out to test whether there are modality-specific modules for spatial and nonspatial memory processing in prefrontal cortex predicated on my hypotheses (Goldman-Rakic, 1987). [Although the predictions would not be altered in the present study, it should be clarified that my topographic model does not refer to stimulus modality but...]
rather to information processing domains (Goldman-Rakic, 1987, 1996a,b). Thus the spatial domain could in principle be engaged by auditory (Vaadia et al., 1986) and somesthetic, as well as visual, processing.) Only Experiment 3 will be considered here because it was the only experiment of three that equated the difficulty of the spatial and nonspatial n-back tasks (by comparing a spatial 3-back task with a nonspatial object 2-back task). (Experiments 1 and 2 had been compromised by the unequal sensory stimulation and/or difficulty between the two tasks as well as power considerations.) However, Experiment 3 had other problems. Only four subjects were tested, there was considerable variability among them, and quantitative group analysis was not performed. Nevertheless, the authors were impressed with the lack of evidence for material-specific dissociations among frontal ROIs and concluded that there was none. Whether a meta-analysis of three studies, two of which had significant design problems and one so lacking in power, can negate positive findings such as those obtained by Haxby et al. seems problematic. Nevertheless, the tendency of shape stimuli to activate the same or overlapping areas, whether their shape or location is to be recalled, is a persistent problem in neurocognitive studies and a source of confusion that needs to be addressed. Some of the factors that could contribute to discrepancies in the experimental results or in interpretation of experiments have been discussed throughout this issue. In the last section of this commentary a few more factors that should also be considered will be mentioned.

The final study to address the issue of spatial/nonspatial modular organization is reported by Stern et al. in this volume. The main objection of this study to specification theory is that a task designed to engage a "monitoring" process activated mid-dorsolateral prefrontal cortex compared to a task that required ordering the sequence of item presentation in working memory. In the latter task, three stimuli were randomly drawn from a set of four with which the subjects had been trained. In the monitoring task, the order of item presentation was identical to that in the former task, but after a delay, only two of the three objects reappeared with a third familiar object (from the set of four) that had not been shown in the sequence. The subjects had to remember which of the objects had been presented in order to identify one that had not. Both memory tasks increased signal intensity in mid-dorsolateral prefrontal cortex bilaterally (areas 46/9) and right ventrolateral frontal cortex (area 44/45). But only the mid-dorsolateral area had greater signal intensity in favor of the monitoring task, which was apparently more demanding, when the two tasks were compared. The interpretation given to the result is somewhat circular, however. Since the task was defined as involving "monitoring," the higher activation is attributed to "monitoring." However, there are great similarities between the tasks and a more parsimonious view is that both tasks required detailed visual inspection of non-descript patterns both during stimulus presentation and during the choice period. This may explain the activation of right rather than left ventrolateral areas possibly homologous to an object/face processing area recently identified in the monkey by O'Scalaidhe et al. (1997, 1999) and in close proximity to the face-processing area described in an early study by Courtney et al. (1996). Alternatively, the mid-dorsolateral prefrontal activations may have engaged an object processing area that is very close to the spatial centers of area 46, which may be difficult to resolve topographically even with fMRI. The higher activity of the mid-dorsolateral area in the monitoring task, on the other hand, could reflect the one major processing difference between the task, which is that the latter required accessing a mental image from long-term memory, whereas the sequence task was more strictly a short-term memory task. The accessing of a stimulus from long-term memory may have been another way of enhancing load within the task, as now four items had to be juggled on the mental sketchpad. On an unrelated but key issue of interpretation, the use of the term "monitoring" in this study is confusing as it would imply that monitoring is engaged only when information is retrieved from long-term stores; differing from the general usage of the term, which is "to keep track of, regulate or control" (from Webster's Seventh New Collegiate Dictionary).

In this meaning, any task that requires keeping track of events or sequences is a monitoring task and the two tasks in the Stern et al. study would represent different degrees of monitoring. A more interesting and parsimonious interpretation of the middorsolateral activation during the "monitoring" task is not that it taps a qualitatively distinct process called monitoring but rather that it may require increased retrieval demand.

The main reason for Stern et al. to consider their findings antithetical to domain specificity is that the memoranda they used were abstract patterns, not topographic information, and yet memory of these stimuli activated areas 46/9. Such evidence would be contradictory if area 46/9 were functionally homogeneous, but it is not. At this point, it may be useful to turn to a discussion of the anatomy of the prefrontal cortex, which has not sufficiently entered into any of the factors considered important in these studies.

**HETEROGENEITY OF PREFRONTAL CORTEX AND THE PROBLEM OF SPATIAL RESOLUTION**

Settling the question of localization will require not only precise and replicable spatial resolution but also adequate analysis and reporting of anatomical data. The Stern et al. and Nystrom et al. studies in this volume are the only reports to include specific Talairach coordinates to describe the localization of signifi-
significant voxels related to spatial vs nonspatial processes. The Postle et al. studies employed ROI analysis of large cortical areas (e.g., fusiform and lingual gyri, including portions of areas 18, 19, and 37; dorsolateral cortex encompassing areas 46/9; and all of areas 44, 45, and 47) and reported t values only. Inspecting these coordinates, it is difficult to determine how closely or distant from one another are areas described as dorsolateral prefrontal cortex or middorsolateral prefrontal cortex in the various Results sections of the special issue reports. This issue is intensified when one considers that the coordinates of dorsolateral areas activated by nonspatial stimuli in one study are not the same as in another (cf. Nystrom et al.'s Experiment 3 and those of Stern et al.). Even in the reports which claim that an area is bilaterally activated it is not to be assumed that identical portions of these broad cytoarchitectonic areas are engaged in each hemisphere. Note that in Tables 1 and 2 of the Stern et al. study, the coordinates of significant activations in mid-dorsolateral are very different and asymmetric (see also Nystrom et al.). This introduces substantial confusion with respect to human–nonhuman comparisons and to meta-analyses of studies designed to address the same conceptual issue (e.g., D'Esposito et al., 1998; Owen et al., 1998).

A signal advance attributable to research in nonhuman primates over the past decades has been the fine-grained functional mapping of the cerebral cortex and the realization that cytoarchitectonically defined areas are not homogeneous with respect to circuitry or to physiology. It follows that the terminology, “dorsolateral” or “dorsal prefrontal” cortex, used to refer to the findings in various imaging studies, though convenient, is not specific enough to address topographic issues. In the 1930s the dorsolateral prefrontal cortex of nonhuman primates was treated as a homogeneous entity with respect to delayed-response function. By the mid-1950s Mishkin had demonstrated that the principal sulcus was the focus for delayed-response deficits that had earlier been observed after frontal lobectomies. Goldman et al. (1970) extended this work by showing that the delay period was the key component of this structure–function association and further that lesions in other portions of the dorsolateral were insignificant contributors to this deficit. Much later, it became clear that the caudal and rostral portions of area 46 can be differentiated on a hodological basis, as can the fundus of the sulcus, its dorsal and ventral rim (Cavada and Goldman-Rakic, 1989). It is to be confidently expected that functional specializations will surely follow the lines of these anatomical divisions when the appropriate tests are applied. Most relevant for the present discussion is the recent mapping of circumscribed areas on the inferior convexity abutting the principal sulcus that contains neurons expressing response selectively to pictures of faces. This special-
SEGREGATING MENTAL OPERATIONS

The articles in this volume have covered a number of issues related to experimental design and statistical analysis. I would emphasize just a few other considerations that are not commonly mentioned and are directly relevant to nonhuman–human comparisons. In the physiological mapping studies of the dorsolateral prefrontal cortex, which have formed the basis for the theory of domain-specific architecture of prefrontal cortex, monkeys maintain fixation as a peripheral visual stimulus is presented on the retina. The animal is trained not to foveate the memorandum and eye movements are controlled throughout a trial. The processes of stimulus registration, memory, and pre- and post-saccadic responses are temporally isolated as is their approximate location within the same local circuits (Rao et al., 1999; Constantinidis et al., 1999). The requirement for maintained fixation throughout the delay period helps to disambiguate eye motion and mnemonic processing. In most imaging studies of spatial working memory to date, including those reported in the present volume, the subjects are allowed to foveate the stimulus, or the extent to which they do is not known, even in the spatial condition. It can be questioned whether these memory paradigms are truly spatial or “spatial-enough” paradigms equivalent to those used in monkeys, particularly when the stimuli in “location” tasks are objects or letters.

Second, in nonspatial working memory tasks involving complex pictures or shapes such as Experiment 3 of Stern et al., it must be determined how much processing engages saccades to inspect these stimuli. At least 1/3 of neurons in areas 46 and 8A are preparatory to eye movements and many prefrontal activations may be due to small saccadic eye movements used to inspect the nondescript patterns at presentation and/or in the memory and response periods. In contrast to the argument of Postle et al. on this point that long-duration stimulus presentation (2 s) is a preferred strategy in spatial tasks, it could be argued that 2 s creates more opportunity for interrogatory eye movements. Neurons with small eye-movement fields have been recorded in monkeys in the general region in which both their “monitoring” and their “nonmonitoring” tasks elicited increased signal intensity (Wilson et al., 1994). Thus, in addition to task load, difficulty, etc., the contribution of these uncontrolled components in cognitive tasks—receptive field location of the memoranda and control of eye movements—to findings in the present series of studies has not been evaluated or considered.

Finally, all of the factors mentioned above may be compounded in n-back formats in which the delay between stimuli is relatively short, trials are presented in blocks, and components of response attributable to stimulus, recall, and response preparation cannot be disambiguated. This makes it difficult to determine how much is contributed to signal intensity by the mnemonic component of the task. Failure to dissociate spatial/nonspatial processors may relate to low demand on the mnemonic component. Event-related fMRI may not necessarily completely resolve this problem because, as we have recently determined, the temporal parameters of stimulus presentation and delay can tremendously alter conclusions about what one is measuring (Leung et al., 1999).

INCONSISTENCIES WITHIN THE NONHUMAN PRIMATE LITERATURE: A POSSIBLE RESOLUTION

Assuming for the purposes of argument that there is considerable evidence for such specialization in the nonhuman primate, i.e., that segregation exists as proposed, an easy resolution of the differences between primate neurophysiological data and fMRI imaging in humans could be that the human brain has been endowed by evolutionary pressure with novel, distinctively human cellular and circuit mechanisms. Alternatively, specialization in primate prefrontal cortex can be denied or minimized (e.g., Rao et al., 1997; Rainer et al., 1998a,b). Concordance would then be achieved with the largely negative results in humans. Nyström et al. in this issue took this approach—arguing that there may be equipotentiality of information coding in prefrontal cortex and that prefrontal neurons may be “tuned to represent either the location or the shape of objects (or both) depending on current experimental context.” There is no doubt that an animal can be trained to recognize and remember the shape and the location of an object in a flexible manner, learn rules, anticipate events, program prospective movements, and benefit from experience. However, the results of Rao et al. (1997) and Rainer et al. (1998a,b) notwithstanding, it is an entirely open matter as to the degree to which an individual neuron’s natural preferred direction or stimulus preference can be transfigured by experience. Indeed, this is one more of the unsolved questions that cognitive neurophysiology is obliged and primed to address. A complete resolution to this difficult question will ultimately come in part from knowledge, not now available, on the nature, quantity, and source of anatomical afferents that a given neuron in a given prefrontal location receives. It is not unreasonable to expect that there are constraints on integration imposed by biological structure. Although the recent findings of Rao et al. (1997) would suggest that neurons can process both “what” and “where” information and that such neurons are distributed uniformly throughout the dorsolateral cortex, they did not present anatomical reconstructions of where these cells were located, but indicated in a drawing that many of them were situated in the
posteroventral location near the frontal eye field region where small amplitude saccades are mediated (Bruce and Goldberg, 1985). More significant, since spatial location in this study was indicated by the placement of a 2° × 2° stimulus at 4° from fixation, the only possible integration that could have been performed by neurons examined in that study would have been within central vision, possibly integrating local object and location information, or alternatively, responding to an object within a large asymmetric receptive field (Suzuki and Azuma, 1983).

Importantly, a subsequent study from this group provided an anatomical diagram clearly showing that there is segregation of “where” neurons from neurons inferred (but not directly demonstrated) to integrate location and object features. The location of the electrode penetrations for “where” cells as described by the authors places them near the arcuate sulcus where Wilson et al. (1994), and no doubt others, have observed neurons with small amplitude movement fields (Rainer et al. 1998a). Overall, while heuristic, the evidence for what and where integration across broad domains warrants critical analysis and replication. Our own recent studies of approximately 2000 neurons recorded across wide areas of the prefrontal cortex have found clear dissociations of neuronal specificity for processing spatial and object information. However, we have stressed that a more fundamental determinant of this segregation may be the dimensionality of space itself from central to peripheral vision (Wilson et al., 1994; O'Scalaidhe et al., 1999), and in that sense, specialization of visual processing in prefrontal cortex may be a product of visuospatial topography. In line with this view, the most eccentric locations used in the Rainer et al. study were at 10° from the fovea, at the borderline of what is considered central vision, and the mean eccentricity of receptive fields measured in their study was 4.5°, which would place limits on the degree of integration across space that could be claimed for that study.

At present, the claim that a neuron (in the case of single-unit recording studies) or an area (in the case of human imaging) integrates what and where is far too general a statement and possibly misleading as to the principles to be applied to information processing in prefrontal cortex. It is enormously clear that cortical neurons, including prefrontal neurons, are specialized for integration of information and there is strong evidence that prefrontal neurons are sensorimotor integrators as evidenced by the sensory, mnemonic, and response signals that a single neuron displays. The nature and degree of integration is now available to analysis with modern methods of multi-electrode recording and is currently the focus of intense study in many laboratories.

**CONCLUSION**

When different results are obtained in human and animals, and assuming that there is conservation of neural mechanisms in evolution, it is obvious that the premises, methods, and relationship between findings and conclusions bear careful examination. It is always difficult to interpret negative results but they are nevertheless useful in pointing to the factors which influence outcomes in neuroimaging studies. The authors of this issue should be credited with attacking a difficult issue in human cognition and contributing creative designs and improvements in methodology in this challenging field. The multiple studies of Nystrom et al. and Stern et al. have pointed to the importance of equating task difficulty while Haxby et al. have revealed interesting differentiation of cortical areas based on the temporal characteristics of their involvement in spatial and object processing. D'Esposito et al., have provided evidence that sensory and mnemonic aspects of processing are associated in the human cortex as they are in monkeys. The present commentary has raised other experimental, anatomical, semantic, and conceptual issues from another perspective. Continued dialogue between researchers working at the cellular level and those studying human cognition as exemplified in this timely issue should provide new insights into the important issue of cortical specification and advance the field of cognitive neuroscience.

**REFERENCES**


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