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Activation: Will hot spots get the hot field in hot water?

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"Twinkle, twinkle, little star, how I wonder what you are" (Taylor, 1813). In the sky or elsewhere, bright spots have long captured the imagination, often leading to magical thinking and poetic verse. In the universe of functional imaging, representational schemes have typically depicted areas in the brain with the highest signal values following one or more subtractions or other contrasts as hot spots with the brightest values in a color scheme. Such spots are commonly regarded as activated areas of the brain. To many, the brighter the spot, the greater the activation, and by inference, the greater the functional significance to the behavior under study. Star gazing in the early imaging world often consisted of "peak picking" or identifying the brightest or hottest spots. As the interpretation of functional images has matured, many investigators have moved away from "peak picking" toward notions of brain networks, but this is not always a great departure from earlier conceptualizations because brain networks are often characterized simply as constellations of hot spots. In this special issue on activation, a number of problems with this concept will be discussed as they relate to the problem of establishing brain–behavior relationships.

In the first paper, Sidtis outlines the major assumptions of the activation approach: an experimental task will result in significant increases in blood flow or hemodynamic response, and contrasts between experimental and control conditions will identify signals that are neurophysiologically relevant to the experimental task. Because the activation approach relies on a contrast procedure, it is further assumed that mental processes can be isolated by contrasting imaging conditions, data generated by contrasts have useful measurement properties, and the function of areas identified by a contrast can be interpreted independent of areas eliminated by the contrast. Sidtis points out that the current notion of activation leads to a characterization of brain organization for motor speech control that is at odds with the results of lesion studies. He shows that a performance-based analysis, which does not rely on contrasts, yields functional imaging results that are consistent with lesion studies. Sidtis argues that the contrast approach is flawed and that image data alone, regardless of the contrasts to which they are subjected, do not appear sufficient for mapping functional brain organization.

Next, the neurobiology of cerebral blood flow is considered. In the first of two papers on this topic, Drake and Iadecola provide an overview of functional hyperemia, a term that refers to the processes that link neural activity and cerebral blood flow. The neurovascular unit is central to understanding these processes, and it consists not only of neurons but also of glia and blood vessels. The functioning of the neurovascular unit is complex, influenced by neurotransmitters, neuromodulators, and neuropeptides. Further, different mechanisms are likely to control these functions in different parts of the brain, and the metabolic processes related to blood flow likely change over the time course of a response. In the second paper in this section, Baslow and Guilfoyle focus on one aspect of functional hyperemia, energy demand. They point out that given the time differences between neuronal activity and the hyperemic response, functional imaging can be thought of as capturing the “afterglow” of an information processing event that requires the expenditure of energy. Baslow and Guilfoyle provide an example of how another form of functional imaging, magnetic resonance spectroscopy, may play an increasingly important role, as the technology develops, in understanding neurophysiologic responses thought to be important in brain–behavior relationships. At the very least, these papers should provide a reminder that blood flow and other derived hemodynamic responses are not direct measures of neuronal activity.

In the next section, data from neurologically impaired subjects provide another context for the consideration of brain mapping using functional imaging. Hillis introduces the use of magnetic resonance imaging to study perfusion. She points out that there is a range of reduced cerebral blood flow in which impairment but not neuronal death occurs. The mapping of areas of frank tissue loss, reduced perfusion, and re-perfusion, in conjunction with careful behavioral assessment of subjects with cerebrovascular disease, is another alternative to the activation approach to functional localization. She provides the example of an activation result in the left midfusiform gyrus, frequently cited as evidence for a visual word form area, which was not confirmed by perfusion studies in stroke patients. Hillis goes on to show how perfusion changes can be informative with respect to the evolution of post-stroke aphasic syndromes, how perfusion studies can be useful in chronic aphasia, and how poor perfusion can impact the BOLD response. If one is to use cerebral blood flow as a marker of brain activity in functional imaging, perfusion studies provide critical context for the consideration of activation results.

In the next paper in this section, Chen and Small address the reproducibility of the BOLD response in functional imaging studies. In addition to the obvious reasons to study reproducibility, they point out that the magnitude of the typical BOLD response is not very different from the baseline noise level of a fMRI time series, increasing the importance of this topic. Examining both normal and neurologically impaired subjects, Chen and Small report not only differences in reproducibility between these groups but also differences in group reproducibility effects under different task conditions. These results address not only the question of reproducibility but also the assumptions of task decomposition. This work suggests that the design of experimental tasks to attempt to meet the pure insertion requirement for a subtraction study (i.e., additive conditions that do not interact) may lead to unpredictable changes in the reliability of the results, which will not be uniform across different study populations.

The next paper touches on several of the key issues in the growing field of data analysis. Hansen distinguishes between contrast-based techniques and “mind reading” techniques. He points out that both generalizability and interpretability are important in models of imaging data, which can be parametric, non-parametric, or semi-parametric. Hansen notes that data reduction in modeling is meaningful if the dominant effects are those induced by the stimulus. Understanding this relationship between the stimulus and image data is at the core of the difference between image processing and establishing brain–behavior relationships. Hansen goes on to demonstrate very different response patterns produced by linear and non-linear models applied to the same data. There are several important general points to be considered. Among them, imaging results are model dependent and the contrast-based activation model is only one of a growing number of approaches.

The final two papers address issues related to the use of functional imaging to study brain organization at a systems level. In the first of these, Eidelberg discusses the application of spatial covariance rather than activation methods to the analysis of functional imaging data obtained from subjects suffering from Parkinson's disease. He has identified a disease-related pattern of activity in this disorder and has studied changes in this pattern with disease progression and treatment. Eidelberg has also studied the effects of performing different tasks on patterns of functional brain activity in Parkinson's disease. This paper provides an example of how a systems approach to functional imaging data can be successfully applied in a situation where the underlying neurologic system is known. The neuropathophysiology of Parkinson's disease is tangible and relatively well understood, so an independent source of data can be referred to in the process of understanding the functional imaging results. As the final paper by Van Lancker Sidtis argues, this is in sharp contrast to the context in which functional imaging studies of language are conducted.

Van Lancker Sidtis points out that neurolinguistic theories do not provide a viable foundation for a rational interpretation of activation results in language studies, in part, because there have been serious problems in demonstrating that linguistic theories have any status in either the structural or functional organization of the brain. The aphasiological approach to characterizing relationships between brain and language is based primarily on production modes (e.g., production, comprehension, and repetition) and naming, which are not central to linguistic models. Because of this, linguistic theory cannot provide the basis for functional imaging studies of language in the same way that the basal ganglia pathophysiology provides a basis for functional imaging studies in Parkinson's disease. On the other side of the equation, Van Lancker Sidtis points out that activation studies cannot reliably inform the development of neurolinguistic theory because the meaning of the functional imaging signals is not well understood and the standard interpretation of activation results leads to conclusions that are incompatible with the results of lesion studies. This is particularly true with respect to the laterality (or bilaterality) of activations in language studies. Because most investigators simply accept the presence of an activation result as a sign of relevant function in a brain area, there is a long list of explanations of right hemisphere activations for functions long regarded as represented in the left hemisphere, a situation that Van Lancker Sidtis refers to as “rich interpretation.” She concludes her paper with the hope that the current situation will lead to a reevaluation of the brain and language representation problem and that new functional imaging approaches may provide a novel view of how language is represented in the brain that is neither aphasiologic nor neurolinguistic by current standards.

A number of important issues regarding activation remain to be addressed. Temporal effects, both short term (over the course of a scanning session) and long term, need to be understood not only with respect to reproducibility but also to gain a better understanding of how the sensitivity of imaging techniques changes with phenomena such as familiarization, practice, and set. The separation of global and regional effects requires explicit consideration, especially for fMRI techniques. The effects of optimizing image processing methods to maintain the most prominent signals in the dataset (hot spots) at the expense of smaller and possibly less stable signals that nevertheless may be functionally significant need to be examined, as do the effects of warping functional data for voxel-based contrasts. The scale properties and response characteristics of blood flow and other hemodynamic responses across different regions of the brain under different performance demands must be characterized as well.

With respect to brain–behavior relationships, the information represented in functional images needs to be evaluated without the assumptions of the activation approach. Not only can high levels of signal be important, but low levels of signal can be important as well. From a systems perspective, the relationships among multiple regions must be considered, and considered not only as a function of a contrast between two (or more) conditions. The problem is finding the function in functional images. Where are the important signals? What are the properties of these signals? What are their response characteristics? Can they be represented as a system? How generalized are these response features across similar behaviors? Just as an understanding of the cosmos has evolved to looking beyond the bright spots in the sky, understanding brain–behavior relationships with functional imaging will have to appreciate the significance of a wider range of signals, including those that are faint, transient, and periodic. The properties of these signals need to be understood before image contrasts are interpretable, and the interplay among signals is likely to be at least as important as the signals themselves. It is time for functional imaging to go beyond admiring the hot spots.

References

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