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Commentary

Improving functional imaging techniques: The dream of a single image for a single mental event

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Understanding the neurobiology of mind processes has become again a central theme of scientific inquiry and it is apparent that progress in both structural and functional imaging techniques has played a key role in the revival of interest in the topic. In this issue, Buckner and colleagues (1) report a promising refinement of one of these techniques that is likely to open new experimental possibilities.

The attempt to understand the neural underpinnings of cognition began in earnest, almost a century and a half ago, with the discovery that the left cerebral hemisphere of humans was related to language and that different aspects of language appear to depend on different sectors of that same hemisphere. Comparable discoveries followed, but they were few and far between, and it was not until the last decade that cognitive neuroscience, the loose coalition of disciplines interested in these issues, came into its own and began expanding rapidly. The practical and theoretical maturity of both psychology and neurobiology certainly had much to do with supporting this new development, but it is possible that, all things being equal, the spectacular growth of cognitive neuroscience might not have happened without a number of rapidly introduced technological advances in neuroimaging. Less than 10 years after computerized x-ray tomography became available, magnetic resonance imaging was introduced for human studies. Until then a true lesion approach had been hampered by the vagaries or absence of postmortem studies in humans. But now the lesion approach had become feasible in the living neurological patient, and acquired brain lesions could be used as experimental probes to investigate hypotheses about the relationship between large-scale neural systems and cognitive processes (2, 3). The revitalized lesion method became the cornerstone of cognitive neuroscience, but it was easy to recognize that brain lesions have limitations: they are hardly ever as small as one would wish, they rarely allow the subject to be his own control, and they fail to capture the temporal dimension of phenomena. These perceived limitations of the lesion method provided a strong incentive for the parallel development of functional imaging, which offered a new means of studying the dynamic neural correlates of cognitive processes in normal humans. Two key techniques were developed: positron-emission tomography (PET) and functional magnetic resonance imaging (fMRI).

The images generated by PET represent physiological parameters, such as the rate of glucose uptake or the rate of blood flow, which are inferred from the distribution of positron-emitting radiopharmaceuticals (4). The value of these images is rooted in the dynamic relationship of these physiologic processes to local neural activity. Thus, increases in *local* synaptic activity generate increases in *local* glucose uptake and blood flow (5–8). The workhorse of human neuroimaging studies, the *activation* experiment, is based on this relationship. Human subjects are requested to perform mental tasks. The neural structures which become active in connection with the performance are identified as a consequence of the coupled metabolic process. Using PET activation, it was relatively easy to demonstrate the physiological correlates of basic motor and sensory processes (9), because of the large magnitude of the effects and because a sizable body of knowledge gathered from other sources was available to validate the results. But the application of the method to the study of complex cognitive processes encountered several predictable hurdles. The first was overcome with the development of the $H_2{}^{15}O$ autoradiographic technique, the short half-life of ^{15}O permitting both successive measurements of cerebral blood flow in a single session and the acquisition of experimental and control images with the same subject (10). This development paved the way for a groundbreaking study, focused on the regional blood flow correlates of the repeated processing of single words (11).

Yet even as the opportunity to measure physiologic correlates of normal cognitive processes arose, cognitive neuroscientists were aware of the significant limitations of PET techniques. For example, PET activation images have poor spatial resolution compared with the structural images that can be obtained from T_1-weighted magnetic resonance imaging. Although it might be thought that technical factors such as the physics of positron decay and annihilation limit the spatial resolution of activation PET, it turns out that a major limiting factor is the low signal-to-noise ratio in the activation images. The analysis of PET activation images actually proceeds at a far *lower* resolution than that which modern tomographs can achieve, essentially trading off spatial resolution for improved signal-to-noise ratio (12). An even greater limitation of PET activation imaging is that tracer kinetics and the relatively poor counting statistics of PET tomographs necessitate that each experimental measurement be integrated over a time period of about 40 seconds. Considering that the cognitive processes we must investigate, for instance the recognition of an object or the naming of a person, occur in only a few hundred milliseconds, it is apparent that the temporal resolution of PET is several orders of magnitude slower than the neuronal events of interest. The attempt to capture such rapid events, however indirectly, led to PET experimental designs which called for *repetitive* performance of a task, and in fact repeated task performance became a standard feature of functional imaging studies. Task repetition takes two forms: repetitive performance within the period of time in which a single measurement is taken (e.g., one PET injection or one fMRI acquisition "block"), and repeated blocks of tasks.

In the face of these challenges, as investigators were optimizing the use of PET, a technological advance with another imaging approach came to the fore: fMRI. It was demonstrated that the magnetic resonance signal could be made sensitive to changes in blood flow and blood oxygenation (13–15). Echoplanar readout technology was developed, permitting the acquisition of magnetic resonance images every 50 msec—i.e., on the same order of magnitude as neural processes (16). These largely unanticipated developments led, perhaps inevitably, to the sense that *the* method of choice had been found, and that human cognition could now be investigated with both high spatial and high temporal resolution. Moreover, such investigation might be accomplished without radionuclides and with a technology vastly more accessible than PET. Future technical advances would be software-driven as often as hardware-driven. In short, fMRI promised the ideal situa-

tion for the cognitive neuroscientist: real-time correlates, accessibility, relatively low cost, no radiation, and no doctors.

It is fair to say that fMRI has delivered substantially on some of these promises, but important to note that it has not met all the expectations. In its present form fMRI cannot exploit the temporal resolution that echoplanar technology affords, and, after all is said and done, its current limitations are not greatly different from those of $H_2[^{15}O]O$ PET. First, despite the frequency with which data can be read out in fMRI, the currently measured parameters are tied to hemodynamic events which are coupled only indirectly to the underlying neural processes. As Buckner *et al.* (1) point out, the local hemodynamic response to activation is slow, on the order of 5–8 sec (15), and the temporal resolution of fMRI is ultimately limited by this hemodynamic filter. Second, signal-to-noise ratios in fMRI are low, necessitating signal averaging techniques not unlike those employed in PET studies. Repeated task performance is a standard feature of experimental design in *both* PET and fMRI studies.

Against this background, it is perhaps easier to appreciate the value of the contribution made by Buckner and colleagues. Buckner *et al.* (1) demonstrate convincingly that individual measurements in fMRI can be made without a need to perform a block of repeated tasks. The advance they propose has an important application: the ability to sort trials *post facto* by subject performance, an analysis that is difficult to achieve with a blocked task design. Their advance will also permit the analysis of the time course of activation after individual stimuli, within the limitations imposed by the hemodynamic response function and, in yet another application, may be used for the comparison analysis of performance trials that differ along several dimensions. It should be noted, however, that the technique proposed by Buckner and colleagues does *not* obviate the need for averaging over successive trials. Indeed, the price paid by reducing the size of a "block" to a single performance is the need to acquire and average over more blocks. Thus, the advantage of the technique is not in the avoidance of the effects of repeated performance, which remain incompletely understood, but in greater flexibility in experimental design.

Progress in understanding human cognition by using functional imaging has been slow for a variety of other reasons, several of which will resist the type of technical improvements discussed above. For instance, no gold standards were available with which to evaluate early functional imaging results, which were not readily reproduced across centers (17–20). New methods of statistical analysis had to be developed to cope with functional imaging data sets (12, 21, 22). The solutions to this problem have taken radically different forms in different centers, leading to uncertainty about the comparability of their results. It is now becoming clear that, although the results of functional imaging studies are reproducible when experimental design is preserved meticulously (11, 23, 24), they are critically sensitive to changes in design, such as the rate at which stimuli are presented (25). On the one hand, this very sensitivity promises powerful future applications of functional imaging, but on the other, it indicates that additional time and effort will be required to define the relevant factors. The problem of stability of the results is compounded by the necessity of comparing the blood flow correlates of all experimental tasks to the correlates of control tasks, rather than to a standard (inactive) state (26, 27). The choice of a suitable and valid control condition is one of the most important steps in experimental design for functional imaging, and there has been little incentive to investigate the consequences of such choices and the means to optimize them. The rapid cycling of functional technology with its immediate promise of improved data quality has effectively diverted attention from these issues. In fact, functional imaging is a moving target, consistently exceeding expectations and advancing technically faster than the results it generates can be integrated within existing bodies of knowledge.

Nonetheless, fMRI technology now allows for the application of more human and technical resources to these problems than ever before. The technique described by Buckner and colleagues constitutes another advance for fMRI, one that could be cleverly exploited by investigators to ask new questions about the physiologic correlates of human cognition. Meanwhile, the imaging of the neural correlates of single and discrete mental events, such as *one* image or *one* word, remains a most desirable dream.

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