A Madness to the Methods in Cognitive Neuroscience?

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Since Paul Broca, the relationship between mind and brain has been the central preoccupation of cognitive neuroscience. In the 19th century, recognition that mental faculties might be understood by observations of individuals with brain damage led to vigorous debates about the properties of mind. By the end of the First World War, neurologists had outlined basic frameworks for the neural organization of language, perception, and motor cognition. Geschwind revived these frameworks in the 1960s and by the 1980s, lesion studies had incorporated methods from experimental psychology, models from cognitive science, formalities from computational approaches, and early developments in structural brain imaging. Around the same time, functional neuroimaging entered the scene. Early xenon probes evolved to the present-day wonders of BOLD and perfusion imaging. In a quick two decades, driven by these technical advances, centers for cognitive neuroscience now dot the landscape, journals such as this one are thriving, and the annual meeting of the Society for Cognitive Neuroscience is overflowing.

In these heady times, a group of young cognitive neuroscientists training at a center in which human lesion studies and functional neuroimaging are pursued with similar vigor inquire about the relative impact of these two methods on the field. Fellows and colleagues, in their article titled ''Method matters: An empirical study of impact on cognitive neuroscience,'' point out that the nature of the evidence derived from the two methods are different. Importantly, they have complementary strengths and weaknesses. A critical difference highlighted in their article is that functional imaging by necessity provides correlational data, whereas lesion studies can support necessity claims for a specific brain region in a particular function.

The authors hypothesize that despite the obvious growth of functional imaging in the last decade or so, lesion studies would have a disproportionate impact on cognitive neuroscience because they offer the possibility of establishing a causal role for structure in behavior in a way that is difficult to establish using functional imaging. The authors did not confirm this hypothesis. Using bibliometric methods, they found that functional imaging studies were cited three times as often as lesion studies, in large part because imaging studies were more likely to be published in high-impact journals. Given the complementary nature of the evidence from both methods, they anticipated extensive cross-method references. However, they found a within-method bias to citations generally, and, furthermore, functional imaging articles cited lesion studies considerably less often than the converse.

To confirm the trends indicated by Fellows and colleagues, I looked at the distribution of cognitive neuroscience methods in the abstracts accepted for the 2005 Annual Meeting of the Cognitive Neuroscience Society (see Figure 1). Imaging studies composed over a third of all abstracts, followed by electrophysiological studies, the bulk of which were event-related potential (ERP) and magnetoencephalogram (MEG) studies. Studies that used patient populations composed 16% of the abstracts. The patient studies were almost evenly split between those focused on understanding a disease (47%), such as autism or schizophrenia, and those in which structure–function relationships were a consideration (53%). These observations do not speak of the final impact of these studies, but they do point out the relative lack of patient-based studies, particularly those addressing basic cognitive neuroscience questions.

Fellows and colleagues pose the following question: Despite the greater ''in-principle'' inferential strength of lesion than functional imaging studies, why in practice do they have less impact on the field? They suggest that sociologic and practical considerations, rather than scientific merit, might be at play. Here, I offer my speculations on the factors that contribute to the relative impact of these methods. These speculations are not intended to be comprehensive. Rather they are intended to begin conversations in response to the question posed by Fellows and colleagues. In my view, the disproportionate impact of functional imaging compared to lesion studies is driven by three factors: the appeal of novelty and technology, by ease of access to neural data, and, in a subtle way, to the pragmatics of hypothesis testing.

First, novelty is intrinsically appealing. As a clinician, I often encounter patients requesting the latest medications, even when they are more expensive and not demonstrably better than older ones. As scions of the enlightenment, many of us believe in progress, and that things newer are generally things better. Lesion studies have been around for a century and a half. Any advances made now are likely to be incremental. By contrast, functional imaging is truly a new way to examine the

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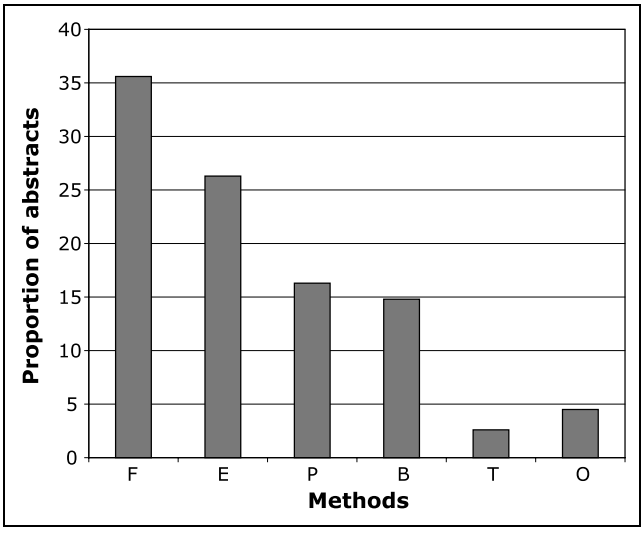

Figure 1. Distribution of methods used in the abstracts accepted for the 2005 Annual Meeting of the Cognitive Neuroscience Society. F = functional imaging, E = electrophysiologic studies including ERP and MEG, P = patient studies, B = behavioral studies, T = TMS studies, O = other, which includes modeling, pharmacologic manipulations, behavioral genetics, and anatomic studies.

brain. The technological advances underlying functional imaging are impressive and the possibility of observing neurophysiological processes in cognition is wondrous. Functional imaging is given the imprimatur of ''big science'' with human brain mapping projects competing with human genome projects for public excitement. If conducting functional imaging research requires substantial financial investment, mobilization of physicists, engineers, and computer scientists in the service of cognitive neuroscience, then surely this approach pays rich dividends in advancing knowledge of brain-behavior relationships.

Second, conducting cognitive neuroscience research is predicated on having access to data about the brain. Clinicians have historically controlled access to patients. Conducting such research is not easy. The obstacles of finding patients, following them, and continuing to make use of this population, which in general suffers from ill health, are substantial. The current regulatory burdens on conducting patient research do not make it any easier. Not many cognitive neuroscientists have access to patient populations for research. By contrast, after the start-up investment for an imaging center, access to neural data is relatively easy. The number of cognitive neuroscience laboratories currently conducting imaging research probably outnumbers substantially the laboratories conducting programmatic lesion studies. The sheer mass of imaging research reinforces its importance.

The impact of imaging on cognitive neuroscience has pervasive and reifying consequences. Most cognitive neuroscience graduate student applicants are interested in learning imaging methods and faculty positions are more likely to advertise for imagers. Editorial boards of influential journals and grant review panels[1] are more likely to have imaging experts than those experienced in lesion studies. In some circles, functional imaging is considered the sine qua non of cognitive neuroscience. It appears that a paradigmatic advance in methods is being taken for a paradigmatic shift in understanding.[2]

Fellows and colleagues suggest that funding agencies and editorial boards might examine their practices in bringing converging evidence to bear on topics of interest. Such an examination would be welcome. As someone weaned on lesion studies (but now also conducting imaging studies) I am deeply sympathetic to their position. Fellows and colleagues emphasize that the great inferential strength of lesion studies is the possibility of establishing a causal role for neural structures in function. However, it is worth asking how well this ''in-principle'' strength has been cashed out in practice?

The third reason for the disproportionate impact of imaging over lesion studies, I suggest lies in the nature of hypothesis testing, which generally focuses on structure or on function.[3] That is, one either takes a fairly well-understood function or process and tests hypotheses of whether specific neural structures are necessary for that process, or one has fairly well-delineated lesions (or patient groups) and tests hypothesis of specific functions for those regions. Probes for structure and function are frequently bootstrapped, but the actual hypothesis testing ultimately tilts in one or the other direction. Historically, lesion studies have had their deepest impact on our understanding of the functional architecture of cognition, often with little regard to structure. The organization of memory and semantic systems, mechanisms involved in reading, the complexities of motor cognition, and the relationship of attention and awareness are a few of the areas informed by lesion studies. Without a nuanced view of the functional architecture of cognition, questions about structure reduce to simple-minded phrenology. Herein lies a paradox about lesion studies. In principle, they have great inferential strengths in understanding structure, whereas in practice their great strength has been in probing function.

When lesion studies do focus on structure, the potential inferential strength of the method has been limited by a lack of statistical muscle needed to support those inferences. The most common method has been to take lesions of a fairly homogenous group of patients, transfer these lesions onto a standard template, and examine areas of maximum overlap in structural damage. This approach has been quite successful in establishing a first approximation of the structures necessary for certain functions. However, it ignores the frequency with which damage to these areas occur without producing the functional deficit in question, and it is complicated by the fact that lesion

locations (at least those produced by stroke) follow vascular rather than neural anatomy. Adjoining regions that might have quite different functions may be damaged together, and different brain regions are not sampled randomly. There are further problems of noisy data. Lesion mapping methods and reliability may be idiosyncratic to different research centers, and because chronic lesions produce significant physical distortions, this problem may not be helped by fully automated protocols. The effects of subtle white matter damage, age, and premorbid experiences on functional–anatomic reorganization are not well understood.

To reiterate a point made by fellows and colleagues, the strengths and weaknesses of lesion and imaging studies are complementary. The point is not to bemoan the impact of imaging studies on cognitive neuroscience as much as to ask how the impact of lesion studies might be enhanced. Many of the reasons that I speculate account for the disproportionate impact of imaging studies could apply to lesions studies. First, the appeal of technological advances in imaging is beginning to be felt in lesion studies. These studies are making use of voxel-based morphometry, perfusion imaging, diffusion tensor imaging, and better lesion registration techniques. Second, better and wider access to patients for research would benefit the field as a whole. Currently, only a few centers are committed to conducting programmatic lesion studies. With appropriate personnel, patient databases can be set up for a fraction of the cost of imaging centers. The dramatic phenomenology of patients with focal brain lesions would undoubtedly attract more investigators, if they could only see these patients. Dissections of this phenomenology has been and will continue to be a rich source from which novel hypotheses are generated. Finally, the statistical constraints in testing structure–function hypotheses in patients are not insurmountable. With sufficient numbers of patients, voxel-based parametric and nonparametric mapping methods from imaging studies could be adapted for lesion studies. These adaptations are beginning to happen and would be accelerated by greater access to patients.

In conclusion, I would like to join Fellows and colleagues in underscoring the importance of converging evidence across methods in cognitive neuroscience. To that I would add that such convergence is most powerful when each method is developed to its full potential. Imaging studies have matured sufficiently that investigations uniquely suited to this method are emerging. Lesion studies, which previously profited from developments in cognitive and computational sciences, are now poised to profit from advances in imaging. As scions of the enlightenment, many of us believe in progress. Things newer might turn out to be things better.

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Notes

1. As an example of the present-day peculiarities of conducting lesion studies, in a competitive renewal of a National Institutes of Health grant investigating unilateral spatial neglect, I was asked by a primary reviewer from a cognitive neuroscience study section to ''justify the use of patients to study the topic in question.''
2. This is not to say that imaging will not make substantial and unique contributions to the field. Early photographers often produced images that mimicked painting to legitimize photography as an art form before establishing a canon of artistic expression that was uniquely suited to the medium. Analogously, hypothesis testing best suited to imaging methods are starting to surface. Questions about the neural bases of individual differences, the neural dynamics of learning over short periods, network properties, and effective connectivity come to mind. Furthermore, the correlational nature of the data itself permits probes of processing within neural structures in ways not possible in lesions studies.
3. This discussion assumes a reductionist/materialist bias in influential scientific journals and funding agencies. That is, ''hard sciences'' are valued over ''soft sciences,'' biology is valued over psychology, and hypotheses about structure are valued over hypotheses about function.