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Functional Biomarkers for Neurodegenerative Disorders Based on the Network Paradigm

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Abstract

This commentary provides a brief introduction to the various uses that functional neuroimaging biomarkers can play in detecting, diagnosing, assessing treatment response and investigating neurodegenerative disorders. It then goes on to explain why the emphasis of much recent work has shifted to network-based biomarkers, as opposed to those that examine individual brain regions. A number of examples are referenced that illustrate the points made.

Introduction

There are three fundamental steps that are necessary for the clinical management of a brain disorder: (1) detection and diagnosis; (2) treatment; and (3) assessment of treatment response. Neurodegenerative disorders are no exception; successful treatment requires prior detection and correct diagnosis. Drugs, surgical intervention, and behavioral therapy remain the major techniques used for treatment of brain disorders, and as a result, these become the targets for much of disease related scientific research. Although the efficacy of these interventions is important in individual patients and clinical trials, it may not always be measured with sensitive or relevant metrics, and therefore neuroscientific investigation addressing these topics remains very important. The fundamental argument made by all the articles in this special issue is that biomarkers will become an increasingly important component of the detection, diagnosis and assessment of treatment of neurodegenerative disorders. In this commentary we will focus on the roles that neuroimaging biomarkers can play, and discuss the advantages of the network paradigm in particular.

What can biomarkers be used for?

For a very long time, behavior was the primary source of information used for detection and diagnosis of neurodegenerative disorders. A person showed up at a clinician's office and complained of some neurological difficulty (e.g., poor memory, aberrant motor functioning). Observation plus some clinical tests were performed, and a preliminary diagnosis was provided. As time went by, the neurodegenerative disorder became worse and the diagnosis became firmer or perhaps changed. There are several problems with this traditional model. Patients often present relatively late when the underlying neuropathology is far advanced;

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e.g., striatal dopamine neuronal loss may exceed 90% before symptoms or diagnosis. Also, the same clinical phenotype may result from very different neuropathological processes; e.g., both tau and ubiquitin pathologies can cause the same clinical picture in frontotemporal dementia. Finally, common clinical measures such as the Mini Mental State Examination may be relatively insensitive to the beneficial effects of disease modifying therapies.

Now, as the articles in this issue make clear, attempts are underway to develop biomarkers for many of the neurodegenerative disorders that have become major societal problems due to the increase in the number of aged individuals. Biomarkers come in four major flavors: blood, cerebrospinal fluid (CSF), genetic analysis and neuroimaging. As discussed by Hampel et al. for Alzheimer's disease (AD) (Hampel et al., 2010), there isn't just one purpose for which a biomarker will be employed; rather, there are numerous and varied uses for which the development of biomarkers is crucial. The four major uses are (1) detection or prediction of a disorder, (2) the differential diagnosis of a disorder, (3) understanding the neural basis of the disorder, and (4) staging a disorder and investigating the efficacy of treatment. The last of these, treatment efficacy, itself has the potential to require a number of separate uses of biomarkers to help address the following: has the treatment reversed the disease process; has it stopped the disease process; has it slowed the spread of the disease; does it facilitate compensatory brain mechanisms? Also, from the point of view of testing treatments, biomarkers have the potential to clean up clinical trials by separating treatment responders from non-responders prior to admission to a clinical trial; to group patients by neuropathology rather than symptoms; and to subtype and/or stratify treatment effects (see the article by Hampel et al. (2011) in this issue for a thorough discussion of the use of biomarkers, including neuroimaging, for Alzheimer disease therapeutic trials). Importantly, a biomarker refers to the underlying disease state, not to the severity of symptoms per se.

Developing and applying biomarkers for the above purposes for any disease can be difficult and complicated. Biological systems are intrinsically nonlinear, which makes understanding their behavior particularly challenging. For the brain, adding to this complexity is the extreme plasticity of neural systems; the brain is a dynamic system that responds to environmental inputs by changing its structure and function (some key words used to describe this are learning and memory). But as well, changes in neural structure and function can occur in response to events occurring within the brain itself, including brain pathology. This represents both good and bad news. For the patient, this plasticity can facilitate functional maintenance or recovery through repair or compensation, or sometimes lead to maladaptive early changes that hinder long term recovery. For the clinician/scientist, the co-evolution of degeneration and compensation introduces ambiguities in the interpretation of biomarkers. This is especially a problem for a neurodegenerative disorder, which can be thought of as a 'slow lesioning' process (i.e., essentially one neuron at a time dies). The slow accumulation of pathology permits compensatory processes to maintain relatively normal brain function for years before behavioral manifestations become clinically noticeable. Thus, this dynamic, adaptive capability of the brain makes every one of the items on the above list of biomarker uses difficult to determine. Nevertheless, because neuroimaging biomarkers are close to the neural substrate, they do allow for a clear and repeatable evaluation of the patient throughout the course of a disease.

Why use network analysis of neuroimaging data?

If one had to summarize neuroscience research in the last fifty years or so, the most general conclusion would be that at every level of research, neural systems have turned out to be more complicated than first thought. To someone entering the field a half century ago, the standard paradigms seemed pretty straight-forward. For example, there was Dale's principle: one neuron, one neurotransmitter. At the macroscopic level, ideas such as functional

segregation prevailed (one brain region, one function). However, research since those halcyon days of yesteryear has shattered most of these notions. The brain is complicated at every level at which it is studied. Thus, it is necessary for brain researchers and clinicians to face up to this and confront the complexity by using more sophisticated research methods and flexible clinical approaches.

Not all the changes will be welcomed. The imposition of traditional cognitive frameworks onto brain imaging data may become redundant, for example in the applications of resting state networks. Or, entrenched cognitive theories may be transcended by new generic principles of brain function, for example predictive coding and the minimization of free energy (Friston and Kiebel, 2009). However, one change that cannot be avoided is the recognition of the importance of neural networks, both to mediate normal brain function and also in terms of network vulnerability to disease. Neuroimaging biomarkers will need to be analyzed more in terms of underlying brain networks, and less in terms of individual regions.

Although the rise of complexity in human neuroscience has many sources, neuroimaging has been of particular importance, especially with regard to understanding brain function. Until the advent of structural and functional brain imaging, most of what we knew about the neural basis of human cognition was primarily derived from neuropsychological investigations of brain damaged subjects, along with studies using electrical stimulation and recording of individuals undergoing neurosurgery. The conclusions drawn were often supplemented and elaborated by investigations in non-human primates and other mammals of their neuroanatomical connections, performance changes produced by focal brain lesions, and electrophysiological microelectrode recordings during specific behavioral tasks (Horwitz et al., 1999). Notice that except for the neuroanatomical connectivity investigations, all these approaches essentially focused on isolated neural objects (e.g., one neuron, one brain region).

Functional neuroimaging, since the 1980s with the expansion of positron emission tomography (PET) and the 1990s with the development of functional magnetic resonance imaging (fMRI), now has become the dominant tool for examining the neural basis of human sensory/motor/cognitive processing. Unlike the other methods denoted above, functional neuroimaging allowed researchers to acquire physiological data from much of the brain simultaneously (although not with particularly high spatial or temporal resolution). These data were often interrogated in terms of functional specialization by evaluating whether a particular brain area showed a significant difference between experimental conditions or between different patient groups. However, they could also be examined in terms of differences in the functional connectivity between two or more brain regions. Some of the early neuroimaging studies used this method to investigate differences in interregional relationships between patients with neurodegenerative disorders and healthy subjects [e.g., (Horwitz et al., 1987; Metter et al., 1984)]. Nevertheless, the standard approach to analyzing neuroimaging data became the examination of individual brain regions via univariate statistical analysis.

In recent years, more and more centers have successfully begun employing formal network analyses as biomarkers of neurodegenerative disease. Network integrity and connectivity can be assessed in many ways [for reviews see Horwitz et al. (2005) and Rowe (2010)]. To understand the choice and interpretation of a given method, some key principles and terms need to be highlighted. The first is the difference between structural and functional connectivity, both of which may be assessed by MRI. Diffusion weighted MRI allows for quantitative or probabilistic tractography, revealing the strength of anatomically defined white matter tracts between cortical and/or subcortical regions [see for example,

Damoiseaux et al. (2009) and Teipel et al. (2010)]. This is distinct from functional connectivity within a brain network, inferred from time-series modeling of fMRI or M/EEG data. Functional connectivity refers to the spatiotemporal covariance of regional neuronal activities, arising from a shared contribution of many distributed brain regions to a common cognitive function. Functional connectivity can apply to many aspects of the neural code, from low frequency fluctuations in regional metabolic demands (fMRI) to transient evoked neurophysiological responses or frequency specific induced oscillations (M/EEG). From neuroimaging, one can even estimate multiple state representations for each part of a network, incorporating excitatory and inhibitory neuronal populations (Marreiros et al., 2008).

A special case of functional connectivity is the causal influence of one region's activity on another, known as effective connectivity, implying directional and causal interactions within a network. Global rather than local network properties may also be characterized, using graph theory to describe the properties of a network's architecture in terms of efficiency or connectedness (Bullmore and Sporns, 2009).

Functional connectivity is often examined using data-driven 'model-independent' multivariate methods such as independent components analysis (ICA) [e.g., (Beckmann et al., 2005)]. Effective connectivity, embodying explicit directional causal connection, is assessed with hypothesis driven methods such as Dynamic Causal Modeling (DCM) (Friston et al., 2003) or structural equation modeling (SEM) (McIntosh and Gonzalez-Lima, 1994; McIntosh et al., 1994). Other methods such psychophysiological interactions (PPI) (Friston et al., 1997) can be used to estimate functional or effective connectivity, depending on a priori assumptions and hypothesis based model specification. Each of these approaches has the potential for use in biomarkers of neurodegenerative disease (Rowe, 2010).

An important distinction in fMRI concerns whether the subjects being scanned are at rest or are performing a task. As the review articles by Bokde et al. (2009) and by Prvulovic et al. (submitted), the latter in this issue, make clear, there has been a surge of interest in performing resting state fMRI studies on brain disorder patients, including those with neurodegenerative disorders, and many of these studies have evaluated functional connectivity. The popularity of resting state fMRI for examining brain disorders is based on the fact that such studies are relatively easy to do and do not require patients to comply with task instructions. Resting state fMRI investigations in healthy subjects have found the presence of a number of distinct networks whose nodes are highly intercorrelated with one another (Beckmann et al., 2005), the most prominent one being the so-called default mode network (DMN) (Greicius et al., 2003; Raichle et al., 2001) whose major nodes consist of posterior cingulate, medial prefrontal cortex, inferior parietal lobule, lateral temporal cortex and hippocampus.

With respect to neurodegenerative disorders, an early resting state study performed with PET showed reduced anterior-posterior functional connectivity in AD patients compared to healthy age-matched controls (Horwitz et al., 1987). More recently, numerous resting state studies using fMRI have been performed in patients with neurodegenerative disorders. Findings include that the DMN changes with aging and AD (Lustig et al., 2003) and is abnormal in mild AD, and in subjects with mild cognitive impairment (Rombouts et al., 2005).

An enigmatic but common feature of neurodegeneration is the selective vulnerability of distributed neuronal subpopulations. Neurodegenerative diseases are rarely focal but progress within non-contiguous but interconnected, brain regions. For instance, using a PET ligand that maps regions of amyloid deposition (PIB), Buckner et al. (2005) demonstrated

that images of amyloid plaques taken at the earliest stages of AD show a distribution quite similar to the DMN. Network imaging analysis therefore has face validity for studying network degenerative disorders, and this clearly represents a major advantage for using a network approach to investigate brain disease.

Returning to the generic roles of biomarkers, there is also evidence that (a) imaging networks is sensitive to the presence of disease, superior to standard imaging methods; (b) network metrics distinguish major alternate diagnoses; (c) imaging networks gives insights into the neuropathophysiology and phenomenology of disease; and (d) imaging networks is sensitive to disease progression and therapy.

Consider first (a) - Network metrics more sensitive than univariate methods in neurodegeneration. A recent example of this was shown by Rowe et al. (2010) who found a lack of significant differences between Parkinson Disease (PD) patients and healthy controls in local activations for action selection, but using DCM, found clear differences in group connectivity patterns. Moreover, the connectivity patterns displayed changes associated with effective dopaminergic therapy.

For (b) - Network metrics distinguish alternate diagnoses – a good example is the paper by Zhou et al. (2010) that used resting state fMRI functional connectivity analysis to contrast two neurodegenerative disorders: behavioral-variant frontotemporal dementia (FTD) and Alzheimer's Disease (AD). They found that AD and FTD have reciprocal effects on two of the major resting state networks, namely the Salience network and Default mode network. This was sufficient to differentially classify individual patients with a very high degree of accuracy.

As an example of (c) - Imaging networks gives insights into the neuropathophysiology and phenomenology of disease – consider the fMRI study of Sonty et al. (2007), in which patients with Primary Progressive Aphasia (PPA) had their fMRI data examined using DCM. The authors found dysfunctional effective connectivity in a language-related network, rather than hypoactivity within specific brain regions, and that the decrement in effective connectivity in this network was predictive of task accuracy. This is an example of a functionally relevant loss of connectivity that leads to performance errors in the PPA patients. As a second example, Grafton et al. (1994), in a PET study, used SEM to perform a network analysis of PD patients following pallidotomy. A key finding was an attenuated thalamocortical connectivity "downstream" from the lesion site. This result illustrates an important point about network behavior: pathology in one part of a network can have effects remote from the affected part. And since most cortical circuits contain recurrent projections, altered connectivity can even appear "upstream" from the lesion site (see the SEM simulation study of Kim and Horwitz (Kim and Horwitz, 2009) for a compelling example of this phenomenon).

Finally, we illustrate (d) - Imaging networks is sensitive to disease progression and therapy. Both the Rowe et al. (2010) and the Grafton et al. (1994) reports, discussed earlier, demonstrate this use of network biomarkers in PD, as does the study by Asanuma et al. (2006). This last investigation found that comparable changes in spatial covariance patterns obtained from PET data occurred with effective treatment by either deep brain stimulation or dopaminergic therapy.

Another important aspect of disease progression follows from our previous comment that neurodegenerative disorders generally take many years of pathology buildup before behavioral manifestations become observable clinically. The question thus arises as to when to begin any treatments (e.g., pharmaceutical intervention) that may be available. Network biomarkers may be useful for this. For AD, suggestions have been made that fMRI resting

state connectivity may be useful for this purpose, given that DMN abnormalities have been found for patients with mild cognitive impairment (Rombouts et al., 2005). However, DMN abnormalities have also been found in young subjects at-risk for AD (i.e., subjects in their 20's), long before these subjects would begin to show behavioral symptoms of AD (Filippini et al., 2009). Should one begin therapy at such an early stage? An alternative strategy would be to scan an at-risk subject nearer to age-of-onset of AD performing a cognitive test that is sensitive to an early dysfunction in the disorder (e.g., memory), and see if the network employed by healthy subjects is being used by the at-risk subject. If it isn't, this may suggest that pathology has now built up to such an extent that treatment is warranted. An example of this type of approach can be found in an SEM PET study of Horwitz et al. (1995). This use of biomarkers is in its infancy, but will likely become the subject of much future research.

Some final comments

In this commentary we have stressed the relatively recent emphasis placed on network analysis of functional neuroimaging data as an important approach for developing biomarkers for various aspects of research on neurodegenerative disorders. As the neuroimaging articles in this issue attest, substantial progress has been made in this endeavor. However, it worth emphasizing that network analysis can be quite difficult because it often entails the application of complex computational tools. Moreover, interpretation of network behavior can be subtle, and even non-intuitive. Finally, this is a field that is undergoing substantial change, with new tools and methods appearing at a rapid pace.

In our view, here are a few of the directions where new methods and issues are likely to develop in the next few years, and these developments could have important consequences for the field of imaging network biomarkers. First, a network consists of a set of nodes connected together by a set of links. In the case of the neuroimaging, the nodes are brain regions. Much of the focus of recent research has been in determining how the brain regions are structurally and/or functionally linked. However, the question of what constitutes a brain region has only recently begun to receive the attention it deserves. Each brain region, even a single voxel, contains multiple neural populations, each conceivably having different functions and different connectivity with other brain regions (e.g., primary visual cortex contains cortical columns with different orientation selectivity, different ocular dominance properties, different sensitivity to color, etc.). Thus, one needs to make sure that the nodes used in each subject's network correspond to the same functional populations, especially when comparing patients against a control population. Such issues are just beginning to be addressed [e.g., (Smith et al., 2010)].

A second issue concerns the fact that fMRI represents neural data with a low temporal resolution. Biomarkers obtained from such data will not be sensitive to important features that occur in the temporal domain of actual neural activity (tens-to-hundreds of milliseconds). We have not said much about EEG or MEG data as sources of useful biomarkers, but research focusing on network analysis of the dynamic data obtained by these methods is continuing apace (e.g., see Wendling et al. (2009) for an overview of some of the methods used in the M/EEG literature to assess connectivity). The translation into clinical biomarkers has been slower than for MRI, but will happen.

A third issue is that the existence of various network metrics could result in interpretational difficulties if the different metrics lead to contradictory conclusions. Different metrics may to sensitive to different aspects of interregional relationships, and there is no *a priori* reason why these relationships should change in the same way for methods that reflect different aspects of neurophysiological coupling (e.g. DCM *versus* SEM *versus* ICA). Moreover,

differences between methods may not be the same in a patient compared to a healthy subject. Thus, research that focuses on understanding the neural basis underlying each network imaging biomarker is essential. The use of large-scale, biologically realistic neural models will be useful in this regard. Such models will be able to simulate functional neuroimaging data which in turn can be analyzed by the various network methods. Unlike actual experimental data, where the underlying neural interrelationships are not known, everything is known in the model, and as such there is a ground truth against which to compare the various biomarker metrics. Examples of this type of research can be found in (Horwitz et al., 2005; Kim and Horwitz, 2009).

In spite of such caveats, a large literature has already developed applying brain connectivity to neuroimaging studies of brain disorders, including neurodegenerative disease (see the Special Topics issue of Frontiers in Systems Neuroscience, edited by B. Horwitz and S. G. Horovitz, on this topic). The network paradigm has arrived, and increasingly it will dominate brain imaging research, forming the basis of biomarker research in neurodegenerative disorders.

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