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Individual Variability in Brain Activity: A Nuisance or an Opportunity?

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Abstract Functional imaging research has been heavily influenced by results based on population-level inference. However, group average results may belie the unique patterns of activity present in the individual that ordinarily are considered random noise. Recent advances in the evolution of MRI hardware have led to significant improvements in the stability and reproducibility of blood oxygen level dependent (BOLD) measurements. These enhancements provide a unique opportunity for closer examination of individual patterns of brain activity. Three objectives can be accomplished by considering brain scans at the individual level; (1) Mapping functional anatomy at a fine grained analysis; (2) Determining if an individual scan is normative with respect to a reference population; and (3) Understanding the sources of intersubject variability in brain activity. In this review, we detail these objectives, briefly discuss their histories and present recent trends in the analyses of individual variability. Finally, we emphasize the unique opportunities and challenges for understanding individual differences through international collaboration among Pacific Rim investigators.

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Introduction

The pursuit to link the mind and the brain has mainly relied on neuroscientific evidence that has examined only those brain processes that are common and universal across individuals. Most current models of brain function are built on commonalities across individuals because the brain is thought to be a noisy system. Yet, while the reliance on commonalities has been a fruitful approach in the basic mapping of the human brain as well as a general understanding of how discrete regions may operate in concert with each other to produce behavior, there are many individual variations of brain function that do not get taken into consideration. Indeed, these variations may be important for a complete understanding of the mind/brain relationship. When investigators examine brain function at the individual level, they often discover that the mind/brain relationship is a highly dynamic process whose patterns across subjects indicate multiple routes through the cortex underlying identical behaviors. However, few theoretical models of brain function incorporate the notion of unique individual variability. Referred to historically as the Robinson Effect (after Robinson 1950), or as the ecological fallacy, aggregate measurements at the group level can (and do) differ in both magnitude and valence relative to individual results. While this effect is familiar to many psychologists, its presence is only now being appreciated in the brain imaging literature.

Indeed, awareness has arisen in cognitive neuroscience that such within-person fluctuations are not strictly random noise, but may rather reflect a by–product of brain

structure, function, and neuromodulation (MacDonald et al. 2006). Several recent studies have examined such candidate sources including white matter (Anstey et al. 2007), genetic alleles (Stefanis et al. 2007), cognitive factors (Thompson-Schill et al. 2005, Kelly et al. 2008), as well as functional correlates of behavioral variability (Bellgrove et al. 2004; MacDonald et al. 2008). The sources present as being highly variable between subjects but highly consistent within individuals (Lovden et al. 2007). We list several of these sources of variability in Table 1.

Over the past two decades functional imaging research based on positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) has been dominated by observations based on population inference. For a given population, how do two tasks compare, or how does a task differ on average for two populations? Results from these comparisons are most often presented as a Student's t-test map of significant activation. This approach accelerated with the development of elegant solutions to combine subject data with stereotaxic alignment, spatial normalization, incorporation of principled group statistics, and control of Type II error. The emphasis on group statistics is well founded if one considers the many factors that can amplify experimental variance and obscure findings at the individual subject level of analysis, as summarized in the examples given in Table 1. We ordinarily assume that the combined effects of these factors result in normally distributed additive random noise in the data. It is assumed that through averaging, the effects of this noise can be removed. On the other hand, recent advances in the evolution of MRI hardware, particularly at 3T and higher, have led to significant improvements in the stability and reproducibility of blood oxygen level dependent (BOLD) measurements. In parallel, sophisticated algorithms for characterizing both gray and white matter brain morphology have motivated detailed characterizations of the interactions between structural morphology and function (Sowell et al. 2008). These advances are setting the stage for new opportunities to study the individual, rather than the group.

Table 1 Sources of variance in functional-anatomic imaging

Anatomy
Cranial shape
Sulcal/Gyral patterning
Volume
Gray matter
White matter
Myelination
CSF
White matter connectivity
Brodmann's areas
Neurotransmitter distribution
Incidental findings
Function
Task paradigm
Cognitive strategy
Performance
Neural-hemodynamic coupling
Functional connectivity
Physiologic noise
Heart rate
Respiration
Measurement
Scanner noise
Imaging Sequence
Data analysis method
Other Factors
Genetics
Experience
Age
Disease

In this review, we consider three objectives linked to individual subject studies: (1) Mapping functional anatomy at a fine grained analysis; (2) Deciding if an individual scan is normative with respect to a reference population; and (3) Understanding the sources of intersubject variability in brain activity. We distinguish these three and briefly discuss their histories and recent trends. We then emphasize the unique opportunities and challenges for understanding individual differences.

Mapping the individual

The main goal of mapping the individual is to identify a close correspondence between cortical anatomy and functional attributes. The outcome of this effort can result in principles of functional anatomy that can then be used to predict functional localization based on anatomy alone. It also leads to the establishment of methods for identifying eloquent brain areas as part of pre-surgical planning (Vinas et al. 1997, Fried 2000). Individual mapping began in the early 1990's when methods for coregistering functional and anatomic scans first became available (Levin et al. 1989). Examples of these early efforts include the definition of normal spatial variability for where to find somatotopically organized body representations in the motor cortex and supplementary motor areas (SMA) in terms of a confidence volume (Grafton et al. 1991, Grafton et al. 1993), the location of the hand area with respect to the "omega" sign in the motor cortex (Yousry et al. 1995), and the localization of area V5 with respect to local sulcal features in the occipitotemporal cortex (Watson et al. 1993). Parallel efforts established that significant brain activation could be identified in patients with neoplasm, vascular malformation (Grafton et al. 1991) and stroke (Cramer et al. 1997) The

early PET efforts have been replaced in large part by fMRI mapping (Krings et al. 2002, Schlosser et al. 2002, Thickbroom et al. 2004, Vlieger et al. 2004), though the same basic principles of combining imaging data from different modalities (BOLD versus T1 anatomy) using rigid body transformations are largely the same. However, with these new fMRI diagnostic studies there exists a persistent challenge of knowing how to interpret a negative scan where there is a lack of activation in an expected brain region (Ulmer et al. 2003, Fujiwara et al. 2004).

Efforts in mapping anatomic features in normal subjects have benefitted from the increasing sensitivity of fMRI. Retinotopic mapping has been frequently performed as a way to map a specific individual's unique visual field prior to the presentation of spatially-based visual stimuli (Tootell et al. 1998). More recent examples include the confirmatory characterization of "Broca's area" as a language area with respect to the fine grained anatomy of pars opercularis in individual subjects. These studies have also incorporated probabilistic maps of cytoarchitechtonics to better link cortical anatomy, function and Brodmann's areas (Amunts et al. 1999, Tomaiuolo et al. 1999). From this there is sufficient evidence to make a strong inference about a functional "hot spot" based on local features of cortical anatomy. Novel methods to identify cytoarchitecture directly from anatomic images (Duyn et al. 2007, Walters et al. 2007) will accelerate this effort and help to alleviate some of the challenges that arise when using post-mortem data to generate probabilistic maps (Eickhoff et al. 2007). Defining function from local anatomy alone has other practical applications. For example, the human homologue of non-human primate area AIP has been localized in the anterior intraparietal sulcus at the individual subject level of analysis (Frey et al. 2005). From this it is possible to localize non-invasive interventions such as transcranial magnetic stimulation based only on anatomic information without the need for additional functional data (Tunik et al. 2005, Rice et al. 2007).

Normative mapping

The primary goal of normative mapping is to define the "normal" form or expression of a variable with respect to a stratified sample of the population. If the anatomy or functional activation of an individual at risk is different in some statistical sense from a reference population then one might consider intervention to correct this discrepancy through treatment options, etc. Computational approaches for processing brain imaging data have been highly important for dealing with the data obtained from large cohorts of subjects to serve as normative groups. Principally, this has concerned the development of non-linear registration techniques, which continues to generate interest since work in this area first began in the early 1990's (Friston et al. 1991, Gholipour et al. 2008). Methods for warping image volumes to known population-based anatomical templates are now routinely invoked in order to factor out the effects of brain size and shape on subsequent functional analyses. Moreover, the fitting of data to a standardized atlas space is important for localizing activation loci to specific coordinates and for the pooling of data across subjects. This has also been motivated by patient diagnosis and the development of methods that characterize the degree of geometric distortion needed to warp a subject into a disease specific standard space and using the distortion parameters as regionally specific indices of brain atrophy (Thompson et al. 2001).

Early diagnostic examples using PET include the identification of resting state mesial temporal hypometabolism to detect possible epileptogenic foci (Engel et al. 1984), resting state hypometabolism in the temporal and parietal cortex of Alzheimer's disease subjects (Foster et al. 1989) and local resting state hypermetabolism in recurrent brain tumors (Di Chiro et al. 1988). More recent efforts have used functional tasks and fMRI to identify a lack of activation in temporal cortex of subjects at risk for Alzheimer's disease (Bookheimer et al. 2000). There is also a long and problematic history of using normative mapping to make claims about an individual subject's mental state or culpibility as part of criminal proceedings and to identify functional deficits in patients with mild brain injury in civil law (Tovino 2007). These claims are usually undermined by a poor match between the individual and the reference population and because there is a lack of adequate control for Type II errors. Finally, there has been a recent interest in developing methods to use an individual subject's fMRI to determine if they are lying or to determine their implicit preference, both forms of "mind reading" (LaConte et al. 2007). These latter methods pose even greater challenges in data modeling and remain largely unproven for individual subject analysis. Potentially, as a result of such concerns, comprehensive databases representing normative variability do not widely exist.

Sources of intersubject variability

The strict reliance upon group averages that is typical in most fMRI investigations may belie the unique patterns of neuroanatomical or functional activation that might be specific to a particular individual. These patterns, like a fingerprint, have certain characteristics which while common to all subjects (e.g. major sulci and gyri), have highly individualized features that contribute to what often is considered as "the noise" surrounding the population mean

(e.g. the inclination and relative depth of a subject's Sylvian fissure; the subject-specific magnitude and extent of BOLD activity). In functional studies, individual patterns of distributed activation may reflect how that brain is uniquely connected for the efficient exchange of cognitive information. For instance, individual variations in the specific location of speech disruption (thought to be Broca's area) has been shown to be predictive of intelligence (Ojemann et al. 2008). Sources of neuroanatomical variability may be related to heritable genetic effects (Blokland et al. 2008), gender (Frost et al. 1999), handedness (Kim et al. 1993), development (Ciesielski et al. 2006), or cultural effects (Morrison et al. 2003). Thus, variations in these patterns are not likely to be entirely random noise but present useful phenotypes or biomarkers for a further examination of individual differences in relation to such variables. Despite these variations, group studies are highly valuable for determining mind/brain relationships and such studies, with carefully constructed samples (stratified as appropriate), will undoubtedly remain invaluable sources of information concerning cognitive processes. We simply argue that these efforts must be combined with careful examinations of the ways in which individuals vary from the group-level expectation and what the possible sources contributing to those variations might be.

Another important source of variation between individuals in a functional activation study is the differential engagement of widespread, universally defined brain regions that is dependent on individual differences in cognitive strategy, style, and tendencies. These variations can affect the topographical pattern of brain activity across the whole brain. Imagine for a moment that all subjects in an fMRI experiment have identical neuroanatomical structures that are precisely the same size and in precisely the same location. However, there may be enormous differences in the strategies that each subject engages in during a particular cognitive task. This may lead to the differential engagement and activation of widespread brain regions. For example, it has been shown in a procedural memory study that slow learners continued to use more areas associated with visuomotor guidance, whereas fast learners shifted to the use of frontal cortex (Grafton et al. 1994). Other recent studies have shown that individual differences in cognitive strategy and capacity activated different regions of the cortex during recognition (Kirchhoff and Buckner 2006) and working memory (Feredoes et al. 2007) tasks. One recent study considered activations unique to individuals and reported that a significant portion of the variability in the topographical pattern of brain activity across the whole brain during a memory task could be explained by individually-specific differences in retrieval strategies (Miller et al. 2002).

An important consideration when evaluating the pattern of activity from a single individual is how stable that pattern of activity is over time. McGonigle and colleagues (2000) scanned one individual in a simple cognitive task in 33 separate sessions. They observed that the variability across sessions was no more than the variability within a session. This relates directly to the manner in which variance is partitioned in the statistical modeling of fMRI activity. The underlying assumption of a random-effects group map is that activity in a particular region that is found in one subject but not the rest of the subjects represents random variation (Friston et al. 1999). However, Miller and colleagues have shown in longitudinal studies that individual patterns of activity are relatively stable over long periods of time (up to several months) despite extensive differences from individual to individual (Miller et al. 2002). In a standard recognition task, for instance, one subject may have activity predominantly in the dorsal regions of the prefrontal and parietal cortex while another subject has activity predominantly in the ventrolateral regions. The individual variations were so extensive that the group map was not representative of the individuals that make up the group map. Yet, by cross correlating the brain volumes across subjects and sessions, Miller and colleagues found that volumes from different sessions of the same subject were twice as similar as volumes from different subjects in the same session.

There are many neuroimaging studies that have examined individual differences in brain activity (for a review see Thompson-Schill et al. 2005, Miller and Van Horn 2007). Many of these studies have shown that the activity in a particular region is modulated by individual differences in performance, which is a very compelling way to demonstrate the function of a given brain region. However, these types of studies rely on a common area of activation across a group of subjects, and only a few studies to our knowledge consider the individual variability and reliability of activity across the whole brain volume (McGonigle et al. 2000, Miller et al., 2002, Feredoes et al. 2007, Seghier et al. 2008). This review focuses on the latter form of variability.

Another distinction we wish to mention is between *intraindividual* variability and *interindividual* variability. In this review, we have focused on interindividual variability, i.e., the variability between subjects. MacDonald and colleagues (2006) recently reviewed intraindividual variability, i.e., the variability within subjects. Previous studies have linked increases in transient, within-subject changes in behavioral performance with aging and other neurodegenerative disorders such as traumatic brain injury and schizophrenia. Further, they have found neuromodulatory correlates of intraindividual variability in behavior using EEG and fMRI. The dynamics and underlying sources of these two forms of variability are likely to be extremely different. While changes in intraindividual variability may reflect changes at the systems or cellular level that are

clinically relevant, interindividual variability may simply reflect basic differences in cognitive processing or physiology between individuals within a normal population, though large interindividual variability has been associated with aging as well (Buckner et al. 2004).

Insight into the sources in interindividual or intersubject variability may be derived from the observation that this kind of variability is particularly pronounced for certain kinds of cognitive tasks, like episodic memory (Miller and Van Horn 2007). Performance on an episodic retrieval task not only relies on components of episodic information, but also elements of non-episodic information (Tulving 1983). Additionally, while episodic memory is known to rely on an extensive hippocampal-cortical network for the consolidation, storage, and utilization of information (Squire et al. 1992, Nadel and Moscovitch 1997, Wittenberg and Tsien 2002), there are also extensive and widespread specialized brain regions not directly related to episodic memory that may nevertheless support and influence episodic memory (Shimamura 1995). These brain regions may or may not be engaged in the task depending on the individual's strategy or traits. Therefore, episodic memory may variably engage several distinct brain regions depending on unique individual strategies or tendencies.

Recent studies that systematically investigate the sources of variability from individual to individual in the topographical pattern of activity during standard episodic memory tasks have revealed that differences in strategy can account for a significant proportion of that variability but not individual differences in memory performance (Miller et al., under review; Donovan et al. 2007). Many other possible factors are still to be explored, such as situational factors (e.g. the influence of experimental design, laboratory environment, stimulus type, state of the subject), cognitive factors (such as other differences in cognitive style or executive functioning ability), physiological factors (such as differences in white matter connectivity, resting state metabolism, or recent caffeine consumption), genetic differences (such as the presence of allelic differences cAMP or FOXP2 or their expression), and personality factors. Some of these factors may be related to specific tasks (such as the differences in memory strategy mentioned above) while other factors may lead to individual deviations that cut across a variety of tasks. A full understanding of the relationship between functional brain activity and task performance will depend on systematic investigations of these fundamental differences.

A new opportunity for international collaboration?

The neuroimaging field has begun to appreciate the importance of individual differences and what it may mean to view each person as having unique and consistent neuroanatomical and functional attributes (Miller et al. 2002). Indeed, as we argue above, individual variability may not simply be noise in the distribution of brain anatomical and functional variables—a nuisance to be controlled for—but, in fact, a valuable opportunity for international research in which cultural contributions to development (Leonard et al. 2006), culture (Hedden et al. 2008), social interaction (Eisenberger et al. 2007), genetic contributions (Bigos and Hariri 2007), and other factors may play a role at the level of the individual.

Given the theme of this special issue, it is worth noting that Pacific Rim researchers have become a source for some of the richest neuroimaging investigations in recent years and are ideally suited to working jointly to examine these effects more closely. For example, recent work by Osaka et al. (2003) examining fMRI data from Japanese subjects has sought to characterize patterns of individual differences in working memory with respect to variability in individual working memory capacity. Examinations of variability in the anatomy of the brain regions most associated with working memory by Fornito et al. (2008) in Australia showed notable correlations between working memory task performance and anatomical variables such as cortical thickness, surface area, and sulcal depth. On the other hand, Chung et al. (2007), in South Korea, have noted that mean signal change, in contrast to spatial extent of activation, was more sensitive to individual variability during visuospatial memory task performance. Tisserand et al. (2005), in Canada, have highlighted the effects of age-related alterations to memory encoding networks that contribute to individual differences in subsequent item recognition. These represent just a few of a number of examples of cognitive neuroscience research from countries around the Pacific that could form the basis for characterizing individual differences over a broad-based population and whose outcomes would stress the importance of cross-cultural collaborative neuroimaging applications.

The sharing of knowledge, data, and new ideas between Pacific Rim partners could do much to shed light on the characteristics of the variability in activity across functional tasks as well as the individually-specific functional connectivity underlying cognitive processing. This does not imply that "Atlantic Rim" collaborations would not be successful in addressing questions of individual variability. Indeed, collaborations involving North American and European partners have already been very successful, for example, in the creation of probabilistic human neuroanatomical atlases encompassing MR and PET approaches (Mazziotta et al. 2001). Yet, as we enter a new era in human brain imaging, existing collaborations between investigators in Asia, Australia, and North American nations might be strengthened and innovative initiatives founded to

specifically examine individual differences in function with respect to language, memory, spatial processing and other cognitive domains. We conclude by suggesting that now is the time for new programs supporting Pacific Rim activities to be developed and encouraged with a view toward taking advantage of emerging techniques and technologies to better understand patterns of individual variability governing cognitive activity.

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