

Individual variability in brain activations associated with episodic retrieval: A role for large-scale databases

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Abstract

The localization of brain functions using neuroimaging techniques is commonly dependent on statistical analyses of groups of subjects in order to identify sites of activation, particularly in studies of episodic memory. Exclusive reliance on group analysis may be to the detriment of understanding the true underlying cognitive nature of brain activations. In this overview, we found that the patterns of brain activity associated with episodic retrieval are very distinct for individual subjects from the patterns of brain activity at the group level. These differences appear to go beyond the relatively small variations due to cytoarchitectonic differences or spatial normalization. We review evidence that individual patterns of brain activity vary widely across subjects and are reliable over time despite extensive variability. We suggest that varied but reliable individual patterns of significant brain activity may be indicative of different cognitive strategies used to produce a recognition response. We argue that individual analyses in conjunction with group analyses are likely to be critical in fully understanding the relationship between retrieval processes and underlying neural systems.

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1. Introduction

The study of individual differences in psychology has a long history. As Thorndike (1911) intoned in his book *Individuality*, “If we could thus adequately describe each of a million human beings, ... the million men would be found to differ widely. Probably no two out of the million would be so alike in mental nature as to be indistinguishable by one who knew their entire natures. Each has an individuality which marks him off from other men. Each has not only a mind, the mind of the human species, but also his own, specialized, particular, readily distinguishable mind. We may study the features of intellect and character which are common to all men, to man as a species; or we may study the differences in intellect and character which distinguish individual men.”

Regarding the mapping of cognitive functions onto specific brain regions, the neurologist Paul Broca argued in the mid-

1800s that speech could be localized to a specific region in the third convolution of the left inferior frontal cortex based on a group of aphasic patients with a common region of brain damage. Around the same time, however, John Hughlings Jackson argued against a centralized region for speech. Jackson focused his studies on individual differences in the aphasic symptoms and in the extent and location of their damage, and he determined from those individual variations that speech was a widely distributed function in the brain (Critchley and Critchley, 1998). Since that time, neuropsychologists have continued to debate the merits of case studies versus group studies of patients in a variety of cognitive domains (Caramazza, 1986; Sokol et al., 1991; Robertson et al., 1993).

Investigators using functional imaging are forced to address a similar issue. Can we make generalizations regarding mind–brain interactions based on group activation maps, and how do we account for individual differences (Grafton et al., 1991, 1994)? Group averaging is a productive technique for localizing brain functions in higher-order cognitive tasks. However, we contend that many brain activations in a higher-order cognitive

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task are uniquely individual and that those unique activations are also critical to the task, and they are often not accounted for because of the reliance on group maps.

Although many neuroimaging studies of individual differences have been conducted, most of these studies have focused on the individual differences in behavior that can account for modulations in a common area of activity. In general, most neuroimaging studies involving individual differences can be divided into five general categories: 1) studies that correlate a particular behavioral performance with modulated activity in a specific brain region; 2) studies that divide subjects into smaller groups based on a behavioral measure and then look for differences in activations between the groups; 3) studies that look at the overlap of individual brain activations and variations of activity around a circumscribed region; 4) studies that look at the degree to which group activations are reproducible; and 5) studies that consider individual variability and reliability of activity across the whole brain volume. We will briefly review the studies in each of these categories, and we will argue that only the fifth category examines unique individual variations across the whole brain that may be critical to our complete understanding of mind/brain interactions.

Several neuroimaging studies have correlated an individual's behavioral performance on a particular task with their brain activity in a particular region, including correlations between: procedural learning and the motor cortex (Grafton et al., 1994), motion detection and Area V5 (Watson et al., 1993), mental imagery and Area 17 (Kosslyn et al., 1996), face perception and the occipital lobe (Alexander et al., 1999), emotional affect and the amygdala (Cahill et al., 1996), visual concept-learning and the left prefrontal cortex (Seger et al., 2000), word recognition and the medial temporal lobe (Nyberg et al., 1996a,b), expertise with novel objects and the middle fusiform "face" area (Gauthier et al., 1999), verbal discrimination and bilateral

prefrontal cortex and temporal regions (Habib et al., 2000), extraversion scores and the amygdala (Canli et al., 2002), negative affect and the ventromedial prefrontal cortex (Zald et al., 2002), semantic encoding strategies and the left prefrontal cortex (Vaidya et al., 2003), and measurements of a persistence trait and midline structures (Gusnard et al., 2003). Mapping parametric modulations in brain activity to differences in performance and task demands have become quite sophisticated and these studies are informative about the functioning of a particular region. But this method of correlating behavior to activity in a particular region still does not take into consideration the activity at the individual level that might not be common to other subjects but is still critical to the performance of a task in that the subject might be using a particular strategy. If a task like episodic retrieval produces many uncommon areas of activity that are stable over time but that do not correlate with performance across a group of subjects, then understanding the factors driving those unique activations may add to our understanding of the relationship between brain activity and the task.

Some neuroimaging studies attempt to investigate individual differences by separating subjects into categories, then examining the group differences in brain activity (Shaywitz et al., 1998; Simos et al., 2002; Osaka et al., 2003). Although valuable information about mind–brain interactions can be obtained with these studies, they are not actually examining individual differences. Instead, they are examining between-group differences, much like a comparison between a patient group and a control group. However, this method can be used in conjunction with individual differences in interesting ways. For example, Grafton et al. (1994) divided subjects on a procedural motor learning task into fast learners and slow learners. They found that individual performance in fast learners was correlated with activity in the frontal lobes and individual

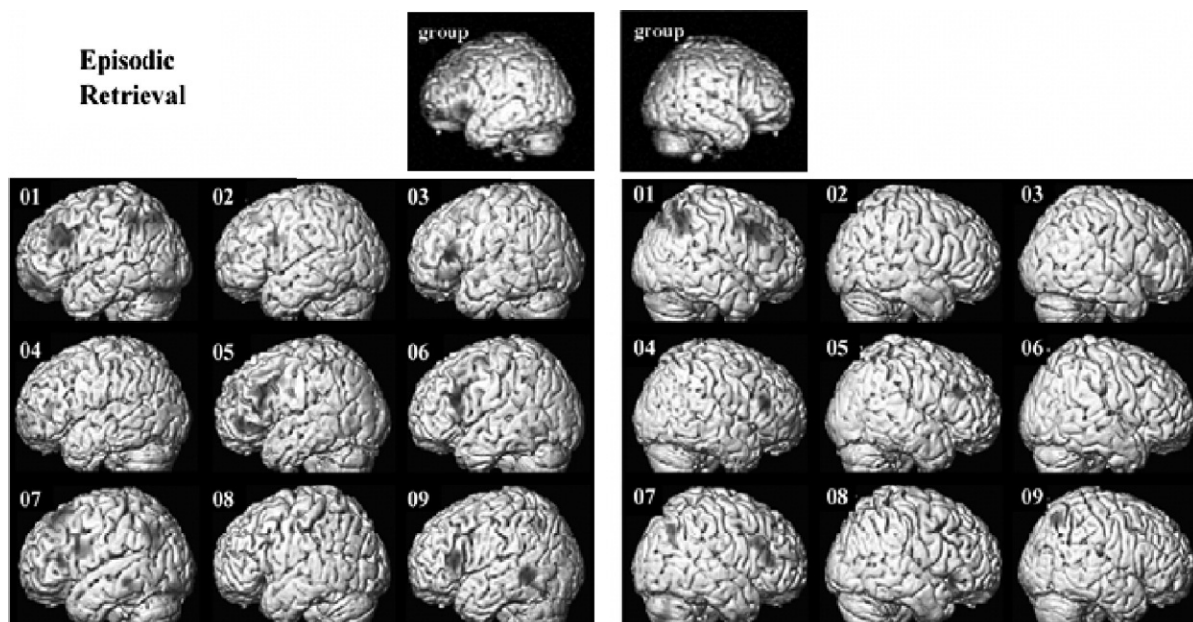


Fig. 1. A comparison of a random-effects group analysis during an episodic retrieval task to individual analyses of four representative subjects in the left (top) and right (bottom) hemispheres (Miller et al., 2002).

performance in slow learners was correlated with activity in the visual cortex.

Other neuroimaging studies highlight individual differences by focusing on the degree of overlap in the activations within a circumscribed region. Grafton et al. (1993) determined peak responses for thumb, finger, wrist, elbow, and shoulder for each individual and determined confidence limits for a response within Talairach space. Klein et al. (2000) were concerned that other neuroimaging studies on mental imagery failed to detect activations in early visual areas because researchers relied on averaging across multiple subjects. Therefore, they analyzed individual subjects and found variability of activations around the calcarine sulcus. Burton et al. (2001) had similar concerns regarding speech production and looked at the variability along the posterior superior temporal gyrus during a word repetition task. Johnson-Frey et al. (2003) also recently conducted a study on motor learning for graspable objects and produced statistical maps that revealed the percentage of overlap between individual activations. These studies are similar to how many patient studies are conducted, identifying common areas of function by displaying the degree of overlap between statistically thresholded activations, or lesion sites in the case of patient studies (Sokol et al., 1991; Robertson et al., 1993). Eventually, such maps of common function could be used to predict individual responses by focusing on individual local gyral anatomy, as has been the case with studies of pointing in individuals (Grafton et al., 1996). These studies are extremely useful in determining common areas of function, and they are effective in demonstrating individual contributions to common sites. However, again, they do not focus on uncommon sites of activation that may or may not overlap with activations from other subjects.

The variability of individual activations associated with episodic retrieval is extensive (Miller et al., 2002). Therefore, we propose that a useful way to understand these brain activations is to consider the unique individual patterns of activation that occur throughout the whole brain. Only a few studies that we know of have attempted to use this approach. McGonigle et al. (2000) examined differences in activations from single subjects across multiple sessions during a motor task, a visual task, and a simple cognitive task. Based on their results, they suggest that multiple sessions for single subjects may be necessary in order to avoid erroneous conclusions about the particular locations of activations based on a single session from multiple subjects. We systematically examined individual variability in brain activations across the whole brain during an episodic retrieval task (Miller et al., 2002). The results revealed two important points about brain activations associated with

episodic retrieval. First, activations produced during episodic retrieval conditions varied significantly from individual to individual, and those activations were not adequately accounted for by group analyses. The differences went well beyond any differences in spatial normalization, and what emerged from the group pattern was a very different brain story than what emerged from the individual patterns (see Fig. 1). Second, despite large variations from subject to subject, those individual patterns of activation were stable over time indicating that those individual activations were more than simply noise (see Fig. 2). The extent to which individual variability in brain activations during any particular cognitive task can be accounted for by cognitive differences versus structural differences has yet to be determined, but episodic retrieval appears to be particularly susceptible to issues of individual variability.

2. Individual variability in brain activations and episodic retrieval

The localization of episodic retrieval across fMRI studies and across subjects within a single study (Miller et al., 2002) is inconsistent. This may in part result from the fact that episodic memory relies on an extensive hippocampal–cortical network for the consolidation, storage, and utilization of information. It has been proposed, on the basis of patient studies and animal models, that the hippocampus is not involved in the permanent storage of information per se, but rather serves to facilitate consolidation of a distributed cortical memory trace (Squire et al., 1992; Wittenberg and Tsien, 2002). A principle characteristic of this distributed network is that it affords the rapid and flexible formation of multimodal memories. Further, in contrast to posterior cortical sites likely to be involved in long-term storage, the prefrontal cortex has been implicated in guiding top-down retrieval of information (Miyashita, 2004). Many memory researchers have suggested that prefrontal and parietal areas support episodic memory with cognitive processes peripheral to the actual retrieval process, including researchers using patient studies (Incisa della Rocchetta and Milner, 1993; Janowsky et al., 1989a,b; Petrides, 1996; Ranganath et al., 2003; Knight, 1991) and neuroimaging studies (Nyberg et al., 1995; Buckner et al., 1998a,b; Rugg et al., 1998; Fletcher et al., 1998; Cabeza et al., 2003; Nölde et al., 1998; Henson et al., 1999a,b; Dobbins, 2001; Dobbins et al., 2003). Moscovitch (1992) referred to this as “working with memory.” Therefore, the emerging picture of episodic retrieval in the brain is that it is comprised of several distinct brain regions. Many of these brain regions, which may be involved in cognitive processing are

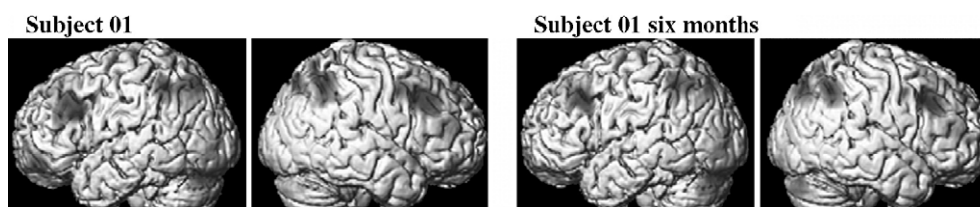


Fig. 2. The left panel is an activation pattern from a single subject during an episodic retrieval tasks, and the right panel is the activation pattern from the same subject performing the same task but six months later (Miller et al., 2002).

peripheral to the actual retrieval of stored information. An individual at a particular time, given the context and strategy of the moment, may differentially engage those different brain regions. One potential implication of this architecture is that one and the same behavioral outcome – such as an “old” response on a recognition test – could be based on a distinct set of information and a distinct combination of neural circuits in two different subjects.

The fact that reported sites of brain activations from past neuroimaging studies of episodic retrieval relying on group analyses have varied greatly from study to study is exemplified by a meta-analysis conducted by Cabeza and Nyberg (2000) that included 52 neuroimaging studies of episodic retrieval. Many of the earlier studies characterized episodic retrieval as a predominantly right anterior prefrontal cortex process. Yet, if we define the right anterior prefrontal cortex as anything in Brodmann Areas 9, 10, 11, or 46, then only 23 out of the 52 studies show activations within that region using group analysis. Several studies show activations exclusively in the left prefrontal cortex. Even when grouping the studies by specific task constraints (e.g., retrieval effort or retrieval mode), very little consistency is shown across studies anywhere in the brain, including the prefrontal cortex and the parietal lobe. In contrast to episodic retrieval, other categories of tasks such as semantic retrieval, episodic encoding, and working memory reveal much more consistency in the reported sites of activations between studies (see Fig. 3). Yet, despite this inconsistency in localization for episodic retrieval studies, only one of the 52 studies showed individual activations (Nolde et al., 1998). The results from our study (Miller et al., 2002) could account for this general inconsistency across studies.

One approach that has been used to deal with the variable nature of episodic retrieval is to constrain the task as much as possible. Indeed, many recent neuroimaging studies of episodic retrieval have attempted to reduce the retrieval task to more specific underlying processes. For example, some studies focus on activity that is higher for responses to old items on a recognition test than responses to new items (referred to as retrieval success), or, the inverse of that, activity that is higher for responses to new items than responses to old items (referred to as retrieval effort) (Buckner et al., 1998a,b; Rugg et al.,

1998). Other studies that have attempted to constrain episodic retrieval into more specific components, such as retrieval mode (Nyberg et al., 1995), production monitoring (Cabeza et al., 2003), retrieval orientation (Nolde et al., 1998; Henson et al., 1999a,b; Dobbins, 2001; Dobbins et al., 2003), and the same maintenance and manipulation of information processes that are used in working memory (Ranganath et al., 2003). Even though there is not always strong agreement in localization across these studies, even with the functional constraints, these attempts using group analyses are quite valid approaches to understanding the various brain components underlying episodic retrieval. However, even if we can derive the specific relationships between brain regions and specific cognitive components, subjects may still engage those specific regions differently depending on their particular strategy. Subjects may indeed have common regions that include specific dorsolateral prefrontal regions for monitoring the retrieval process or anterior prefrontal regions for retrieval effort, but whether or not a subject engages these regions during a retrieval task may depend on their strategy. For example, some subjects may carefully monitor their retrieval output and be very conservative in their responses. Other subjects may simply rely on some graded sense of familiarity and temporal organization and they may be more liberal in their responses. We reason that if individuals can strategically engage these peripheral cognitive processes differentially, then focusing on uncommon activations in individual subjects in an unconstrained way provides a unique opportunity to understand these relationships that add to our knowledge gained by constrained group analysis.

Retrieval strategies during a recognition test can take a variety of forms (Rogers et al., 2000; Graf and Birt, 1996; Reder and Schunn, 1996; Tulving, 1983; Mandler, 1980). For example, one form of a retrieval strategy is to be conservative or liberal in judging a test item as “old” or “new.” Some subjects may be quite conservative in the decision using a strict criterion for judging an item as “old,” while other subjects may be much more liberal in their judgment, replying “old” to any item that seems to be familiar. These individual differences in strategy can easily be measured on a recognition test using Signal Detection Theory (Green and Swets, 1966/1974; Macmillan and Creelman, 1991; Murdock, 1974; Ratcliff et al., 1992;

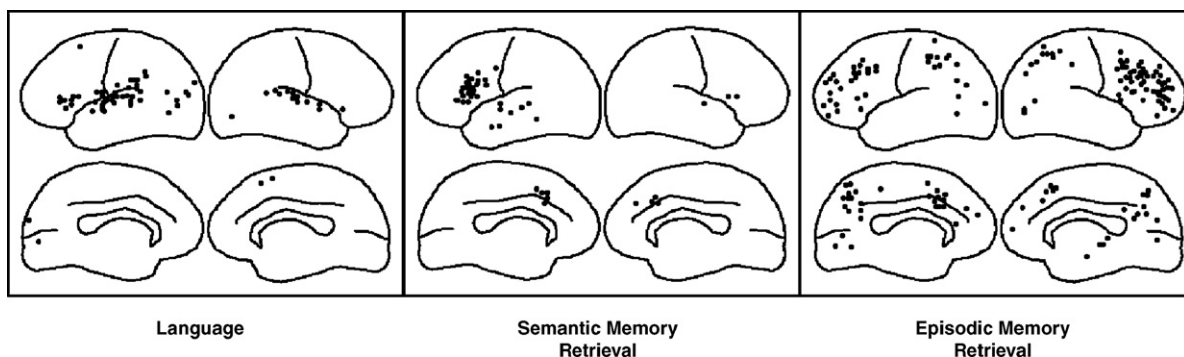


Fig. 3. Reported activations from some of the 275 PET and fMRI studies in 3 representative cognitive domains as presented in the meta-analysis by Cabeza and Nyberg (2000). The black dots represent sites of peak activations from a group analysis reported by each study. Peak activations are shown from 22 studies of language, 28 studies of semantic memory retrieval, and 52 studies of episodic retrieval reported in the published literature.

Yonelinas, 1997; Miller and Wolford, 1999). Another form of retrieval strategy is that some subjects tend to rely on visualization during encoding and retrieval, while other subjects tend to rely on verbalization. Individual differences in this form of strategy may not be readily measured on the basis of “old” and “new” responses to a recognition test, yet they may produce very different patterns of brain activity.

In order to fully understand the brain activations underlying episodic retrieval, it is critical to understand the sources of the individual variability inherent in the task. Individual variability may be due to structural differences, i.e., two individuals think identically but differences in brain architecture and vasculature lead to differences in the patterns of activations. Alternatively, individual variability may be due to cognitive differences, i.e., the brains of two individuals are identical but each individual thinks about the task in a different way leading to different patterns of activations. We think it’s likely to be a combination of both. We argue that new techniques need to be developed to better characterize and analyze individual differences in brain activity, and that individual patterns of activity for many tasks need to be analyzed, reported, and made available to public depositories like the fMRI Data Center.

3. A novel technique for exploring individual differences in brain activity

Many recent advances in image acquisition and processing have improved the signal to noise characteristics in brain mapping studies enhancing our ability to identify reliable responses within individual subjects. Furthermore, many neuroimaging studies now use a random-effects model to produce group activation maps. Random-effects models, in contrast to fixed-effects models, assess the variability in activation effects from subject to subject (Friston et al., 1999). This allows inferences to be made from a group of subjects to the general population. It is often assumed that regions that are significantly active for an individual but are not significantly active for the group using a random-effects model simply reflect noise. If these activations are simply noise, then they should not appear after retesting the same individual in a different session. However, we showed that unique individual activations are stable over time (Miller et al., 2002).

We are not implying that grouping activation across subjects is an invalid method of analysis, nor are we implying that individual analysis is necessarily superior to group analysis. Indeed group analysis can be very informative in identifying common regions of activity for a given task, and there has been much effort in determining the most appropriate method of group analysis for a variety of experimental situations (Friston et al., 1999). After all, it was group analysis in several neuroimaging studies that revealed the critical involvement of the prefrontal cortex in episodic memory that may not have been fully appreciated prior to neuroimaging (Shimamura, 1995; Tulving et al., 1994). We do suggest, however, that reliance on group analysis alone, particularly for higher-order cognitions like episodic retrieval, may be incomplete and, in some cases, misleading. Studies that focus on individual patterns of

activation over time, coupled with group analysis, may be critical to understanding the relationship between memory and brain activity.

A particularly challenging aspect of investigating unique individual patterns of activations is that similarities and differences between individual patterns of brain activations need to be quantified in a way that will not be dependent on any statistical threshold. For example, the individual activation maps shown in Fig. 1 may be more or less similar to each other depending on the statistical threshold that is used to produce those individual patterns of activations. Therefore, we have developed a technique in which brain volumes of raw signal intensity values at each timepoint are cross-correlated with each other after spatial normalization but prior to any statistical threshold. Each timepoint or volume represents an individual subject, a particular study, a specific session, and a cognitive condition. The correlation value that represents how well two particular volumes are correlated with each other can then be coded whether it represents, for example, the same subject or not, same study or not, same session or not, same condition or not, and any interaction between them. The whole matrix of correlation values produced by this cross-correlation can then be submitted to a step-wise multivariate regression analysis in order to determine which variable accounts for most of the variance in correlation values.

We have previously demonstrated the feasibility of this technique in our neuroimaging study of episodic retrieval (Miller et al., 2002). A qualitative look at the individual maps of activations, as shown in Fig. 1, clearly shows a large variation in the patterns of brain activations from subject to subject (so much so that the group map is not representative of the individual maps), yet there is a remarkable consistency within subjects from session to session (even 6 months apart) (Fig. 2). When we sought to quantify this relationship through the cross-correlation of brain volumes of raw signal intensity values, we found that the average correlation within the same subject was .947 while the average correlation between subjects was .729. A step-wise multivariate regression that included six dummy variables accounted for 93% of the variance in the correlation values ($F(6; 114,953)=259, 635.9$). The variables that significantly contributed to the equation were the same subject versus different subjects, same session versus different sessions, same condition versus different conditions, an interaction between the same subject and same session, an interaction between the same subject and same condition, and an interaction between the same session and same condition. Only three of these variables were noticeably accounted for the variance; the same subject ($t=-722.8$) accounted for 61.5% of the variance, the same session ($t=-545.1$) accounted for 5.8% of the variance, and the interaction between the same subject and same session ($t=656.9$) accounted for 25.9% of the variance. The R-squared change for same condition ($t=12.7$), the interaction between same subject and same condition ($t=-12.8$), and the interaction between same session and same condition ($t=-5.9$) was 0. This indicated that even though there is enough power in the general linear model to produce significant differences between experimental conditions when you collapse across subjects,

most of the variance in signal intensities is accounted for by individual subjects. Again, the most significant factor in evaluating the variations in the correlation values was whether the volumes came from the same subject or not, verifying our initial qualitative assessment of the data. There is a lot of information about brain activity at the individual level during an episodic retrieval task that is being lost by relying on group analysis.

4. Future considerations: a role for mining archival resources?

Extensive individual variability in brain activations during higher-order cognitive tasks will come as little surprise to most researchers conducting neuroimaging studies. We have shown that, despite this extensive variability, unique individual patterns of activity are stable over time. However, the sources of this individual variability are not known, and this knowledge may be critical to our complete understanding of the relationship between brain activity and episodic retrieval. The variability may be due to the basic differences in vasculature, or cognitive differences underlying the task. Many other factors may also independently affect the variability of brain activations during a neuroimaging study besides differences in brain structure and cognition. For example, whether the trials of an experiment are randomly presented and temporally jittered to utilize an event-related analysis or blocked by condition can possibly have an effect, as can other less interesting factors such as the strength of the scanner or the time that has elapsed between the first and last subject scanned. Some of these questions may be answered in the future by conducting longitudinal within-subjects fMRI studies. However, these questions can also be addressed by assessing the huge volume and variety of data that is available through the fMRI Data Center.

The fMRI Data Center (Van Horn et al., 2004) currently maintains more than 113 complete fMRI study datasets from published articles representing well over 2500 individual subjects from a broad number of cognitive paradigms. This provides a unique opportunity to test hypotheses on variability in a thorough and systematic way that could not be otherwise accomplished. The fMRIDC receives raw, processed, and result image data sets contributed from the authors of published fMRI studies from the peer-reviewed literature, such as the *Journal of Cognitive Neuroscience*, *The Journal of Neuroscience*, and *The Proceedings of the National Academy of Science*. The fMRI studies range broadly in techniques and in cognitive domains, ranging from lower-order tasks like motor preparation (Toni et al., 2002) and visuospatial processing (Ng et al., 2001) to higher-order tasks like spatial working memory (Leung et al., 2002) and episodic retrieval (Davachi et al., 2001). None of these original studies assessed individual variability. However, each of these studies has deposited raw data from individual subjects that make an analysis of individual variability possible. This presents a potentially valuable resource from which new analyses may be performed to assess the individual variability across the studies.

A number of studies have now appeared that have taken advantage of the fMRIDC as a wide ranging fMRI data resource through which to apply novel data mining and analytic techniques. In one study, Greicius and Menon (2004) explored the evidence for alterations in the brain's metabolic baseline. Using independent component analysis on the fMRI data of Buckner et al. (2000) they were able to detect the full default-mode network in both runs and to demonstrate that, in the majority of subjects, it persisted across both rest and stimulus epochs, uncoupled from the task waveform, and so mostly undetectable as deactivation. Their new analysis showed that the more a subject's default-mode activity was correlated with the rest epochs (and "deactivated" during stimulus epochs), the greater that subject's activation to the visual and auditory stimuli. They conclude that activity in the default-mode network may persist through both experimental and rest epochs if the experiment is not sufficiently challenging. Time series analysis of default-mode activity provides a measure of the degree to which a task engages a subject and whether it is sufficient to interrupt the processes—presumably cognitive, internally-generated, and involving episodic memory—mediated by the default-mode network.

An article by Lloyd (2002) mined the data from four complete fMRI study data sets to investigate temporal components related to human consciousness. This study utilized data from four complete published fMRI studies, representing many gigabytes of data. This study was unique in that consciousness was not something specifically investigated by the authors of the original fMRI investigations. Modern philosophical theories of consciousness posit that traces of its temporal structure must exist in these data and could be retrospectively measured. In particular, Lloyd's analysis revealed evidence of temporal compression of experiential conscious state as it moves from the present and into the past. His analysis noted particular specificity at the single-subject level, in which the profile of consciousness was like an individual fingerprint, unique to each subject, but with the hallmarks of fundamental processes involving memory encoding and consolidation.

Another area of interest to fMRI researchers is that of functional connectivity analysis and large-scale neural modeling (Horwitz et al., 2000), wherein analysis of fMRI data is extended beyond the identification of discrete activation hotspots to that of examining the inter-regional patterns of correlation. These patterns are reflective of the degree to which one brain area is functionally correlated or "wired" with another. Recently, using data obtained through the fMRIDC, Mechelli et al. (2003) estimated neuronal interactions that mediate category effects using a functional connectivity modeling technique called Dynamic Causal Modeling (DCM). They employed a Bayesian framework to estimate and make inferences about the influence that one region exerts over another and how this is affected by experimental changes. They modeled the interactions among brain regions and observed that category effects in occipital and temporal cortex were mediated by inputs from early visual cortex. In contrast, the connectivity from the superior/inferior parietal

area to the category-responsive areas was unaffected by the presentation of chairs, faces, or houses. These counter-intuitive findings indicate that category effects in the occipital and temporal cortex can be mediated by bottom-up, rather than top-down, mechanisms. However, these patterns of connectivity likely possess considerable variation across subjects and would be worthy of more detailed examination at the single-subject level.

Important in measuring statistical power, reproducibility is the extent to which the active status of a voxel remains the same across replicates conducted under the same conditions. Liou et al. (2003) employed an empirically-based Bayesian method for estimating BOLD effects due to experimental stimuli, the threshold optimization procedure for assigning voxels to the active status, and the construction of reproducibility brain maps. They found that subjects in a study obtained via the fMRIDC appeared to exercise more than one mechanism in responding to visual objects when performing alternately matching and passive tasks. One mechanism appeared to evoke BOLD activity in ventromedial temporal areas, in agreement with those reported in the original published article. But some subjects showed additional regions involving the precuneus and posterior cingulate. Overall, the patterns of activity were found to be statistically reproducible in at least 4 out of 6 subjects involved in the experiment. However, the latency between the stimulus presentation and the peak of the hemodynamic response function varied considerably among individual subjects according to the types of stimuli and experimental tasks. Their analysis strongly suggests that the subjects in this experiment exhibited different strategies, recruiting activity in additional regions to simply object specific areas, when making their responses to visual stimuli.

Such re-examinations offer new insights in to previously published neuroimaging data that might not have been possible on the basis of the published journal article alone. Indeed, they may reveal effects not conceived of by the original authors or, perhaps, envisioned by theoreticians. Having the actual data used in published experiments positions researchers to ask novel questions and obtain useful answers without having to collect new data themselves. Further advancements at the fMRIDC will place more data in the hands of more researchers where upon even greater data mining explorations may be undertaken. Finally, cognitive domains such as episodic memory, in which we expect large individual differences, may be ideally suited to examination using fMRI data from the fMRIDC archive.

5. Conclusions

The localization of cognitive operations using functional brain imaging depends greatly upon statistical analyses of groups of subjects in order to identify sites of activation, particularly in studies of episodic memory. Exclusive reliance on group analysis may be to the detriment of understanding the true underlying cognitive nature of brain activations. In the present review, we argue that the patterns of brain activity

associated with many cognitive processes, but in particular, episodic retrieval are often unique to individual subjects and not always reflected in the patterns of brain activity at the group level. This variation appears to extend beyond the relatively small variations due to differences in brain shape or processing methods. This implies that most patterns of BOLD activation are multi-factorial in the context of components due to population level effects and statistical noise but also due to components specific to each subject. These subject-specific factors may be related to the unique manner in which subjects process information, rely on strategy, or other pertinent components. Evidence indicates that individual patterns of brain activity vary widely across subjects but are reliable over time despite this extensive variability. We suggest that varied but consistent individual patterns of significant brain activity may be indicative of different cognitive strategies used to produce a recognition response. Large-scale archives of brain activation, like the fMRIDC, likely hold excellent examples of this subject variation. Mining these studies will help elucidate the degree and extent of variation across subjects and potentially lead to further refinement of thinking in the field about fundamental cognitive operations. Indeed, we encourage more researchers to examine the study data available from this important neuroscience resource. In conclusion, analyses of new and archival single-subject data, in conjunction with group analyses, are likely to be critical in fully understanding the relationship between memory retrieval and other processes and the neural systems that underlie them.

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